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PNEUMONIA DUE TO THE STREPTOCOCCUS VIRIDANS*

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The *Streptococcus viridans* (*Streptococcus alpha*) has up to the present time received little consideration as an etiologic agent in the causation of pneumonia. Careful search through the literature reveals few reports of cases. The relationship of *S. viridans* to subacute bacterial endocarditis is well established. However, when the organism is found in the sputum of pneumonia patients, it is usually considered as either an upper respiratory saprophyte or a laboratory contaminant. It is our impression that in certain instances, the *S. viridans* is the primary cause of pneumonia and in other cases it may play an important rôle as a secondary invader in pneumococcic pneumonia. From the pulmonary focus, it may occasionally invade the blood stream.[9]

The rôle of this organism in the production of pneumonia suggested itself to us during the observation of 2 pneumonia patients who failed to show the usual good response to sulfapyridine therapy and in whom after careful study, it was found that the *S. viridans* was the causative agent. This report concerns 5 cases of pneumonia attributed to the *S. viridans*.† The disease is relatively rare, but this does not diminish the importance of its recognition.

Following are the protocols of the 5 cases which have come under our observation:

Case Histories. Case 1. W. H., white male, age 82, suffered from a chest cold for 3 weeks with cough and expectoration of thick gray sputum. He com-

* These cases were studied as part of an investigation concerning the merits of chemotherapy and combined chemotherapy and serum in the treatment of pneumonia, under the auspices of a Committee for Pneumonia Investigation consisting of Drs. Russell L. Cecil, I. Ogden Woodruff, Asa L. Lincoln and Charles H. Nammack (the latter three, directors of the First, Second and Fourth Medical Divisions, respectively), Norman Plummer, Herbert K. Ensworth, James Liebman, William H. Kammerer and the authors.

† We observed 5 cases of pneumococcic pneumonia whose illness was prolonged by reason of secondary invasion of the infected lung or pleura with this organism.

plained of pain in the left chest, chills, and weakness 5 days before admission. On admission he appeared acutely ill, dehydrated, and dyspneic. There was dullness and bronchial breathing with numerous crepitant râles over the right lower and right middle lobes, and a friction rub was heard in the right axilla. The heart was rapid but not enlarged and no murmurs were heard. No petechiæ were seen and the spleen was not palpable. The white cells on admission numbered 15,700 with 64% young forms of polynuclears, 30% mature forms, 3% monocytes and 3% lymphocytes.

The patient's downhill course was rapid. The temperature was 101.6° F. on admission. It soon rose to 105° and remained around 103° until his death 3 days after he was hospitalized. The sputum was thick, gray and mucoid. Sputum studies on admission and on the following day revealed a pure culture of *S. viridans* (*alpha*). The blood culture yielded a heavy growth of *S. viridans*. Signs of fluid developed at the right base and a thoracentesis 24 hours before death revealed turbid fluid which also showed a pure growth of *S. viridans*. Permission was not obtained for autopsy.

Case 2. W. M. P., a colored, obese female, age 20 who 2 days following a tooth extraction complained of very severe chest pain and dry cough. She was admitted on the 4th day of illness appearing dyspneic and acutely ill with consolidation of the right lower lobe. The heart was normal on repeated examinations. The sputum culture showed *S. viridans* and a few colonies of Type XVII pneumococci. In view of the fact that alternate cases of pneumococcic pneumonia during this season were treated with serum as well as sulfapyridine as part of a controlled study,[5] she received 190,000 units of Type XVII antipneumococcic rabbit serum intravenously with no response. A lung suction on the following day showed a pure culture of *S. viridans*.

The patient received 2 gm. of sulfapyridine immediately on admission followed by 1 gm. every 4 hours for 2 weeks with no improvement, although the level of free sulfapyridine in the blood remained about 5 mg. per 100 cc. The temperature ranged about 102° to 103° and the patient's chief complaint was severe chest pain. The physical signs were those of fluid as well as consolidation and this was confirmed by a Roentgen ray taken on the 13th day of illness. A thoracentesis, however, yielded only 10 cc. of bloody fluid which on culture showed *S. viridans*. The sputum which had been mucopurulent and tenacious became bloody and mucoid but never foul. Sputum culture was repeated on the 6th day and showed *S. viridans* in pure culture.

The white cells numbered 13,400 with 70% polynuclears and 30% lymphocytes on admission but after 2 weeks, the white cells dropped to 6400, with 80% polynuclears.

Blood cultures were persistently negative. The patient remained markedly toxic and febrile. She had a hemoptysis on the 26th day, following which there occurred pulmonary edema and death. Permission for autopsy was refused.

Case 3. M. T., white male, age 59, who had a 2 weeks history of a sore throat followed by weakness, chills, fever and cough with yellow sputum. Two days before admission he noticed difficulty in breathing and heaviness in the chest. He appeared dyspneic and cyanotic and complained of severe chest pain. There were physical and Roentgen ray findings of consolidation of the right lower lobe. Sputum typing by the Neufeld method yielded Types III and XIII pneumococci. A sputum culture however showed the predominant organism to be the *S. viridans*. For the same reason as in Case 2, he received 220,000 units of Type XIII antipneumococcic rabbit serum with no effect. He also received a total of 55 gm. of sulfapyridine over a period of 9 days.

The patient's clinical course was severe. Within a few days the entire right lung became consolidated and he developed fluid at the base. A thoracentesis 8 days after admission yielded 460 cc. of thin yellow fluid. The differential count showed 70% of the cells to be polynuclears and 30% lymphocytes. The only organisms seen on a stained smear were chains of cocci, but culture was sterile. Blood cultures were persistently negative. The patient gradually became more dyspneic, cyanotic and toxic and expired 12 days after admission.

Necropsy showed consolidation of the entire right lung with serofibrinous

pleurisy and bronchopneumonia of the left lower lobe. A postmortem culture of the infected lung yielded the *S. viridans*, no pneumococci being found. The exudate in the involved lung was fibrinous and contained a predominance of lymphocytes. The lumina of the bronchioles contained considerable desquamated epithelium and lymphocytes. The mucosa and submucosa was infiltrated with white cells, mainly lymphocytes. The heart showed no abnormalities.

Case 4. S. L., 52-year-old Chinaman admitted on the 3d day of illness with cough, fever, chills, and severe pain in the right chest. He appeared critically ill, and had consolidation of the right lower lobe. His sputum, was mucoid and thick but not bloody. It was typed both on admission and on 3 occasions subsequently, showing several organisms, *viz.: S. viridans*, and Types II, IX, and XXIX pneumococci.

He received sulfapyridine from the 3d to the 13th day, a total of 42 gm. being given. The temperature fell from 104° to 101° on the 13th day, but apart from this, there was little effect upon the patient's general condition. Type II antipneumococcic rabbit serum was given on the 10th day with no apparent effect. The temperature on the 17th day rose to 104° and the patient had chills. A blood culture taken on the 20th day showed *S. viridans* in the broths.

During the 4th week, the process spread to the left upper lobe. During the same period, thoracentesis of the right pleural cavity done on 2 occasions yielded 150 cc. and 175 cc., respectively, of straw-colored fluid with a specific gravity of 1.015, and a predominance of polynuclear cells in the exudate. Culture of the first specimen yielded *S. viridans*. The second specimen was sterile.

During the 6th week, sulfamethylthiazole was used for 4 days, a total of 16 gm. of the drug being employed with little effect.

The patient ran a prolonged, severe, febrile course. For weeks he was in an exhausted state but eventually he recovered.

Case 5. P. S., a white miner, age 59, with a history of chronic "asthma" who developed severe chills, pleurisy and fever 6 days before admission. He showed signs of partial consolidation of both lower lobes on admission. His sputum was white, mucoid and yielded Types III, XII, and XXXII pneumococci on typing. On the 24th day, his sputum was bloody. Sulfathiazole therapy was started with no effect, although the blood levels ranged between 7 and 10 mg. per 100 cc. The temperature remained between 101° and 102° until the 20th day, following which it began to fluctuate. The patient was severely toxic. There was no evidence of fluid in the chest. There were no cardiac murmurs, no petechiæ, no hematuria and the spleen was not felt. Roentgen rays showed partial consolidation of both lower lobes as well as fibrosis and emphysema.

The blood cultures, which, during the early stages were sterile, yielded *S. viridans* on the 40th day. This organism was tested by Dr. Whelan D. Sutliff in the laboratory of the New York Board of Health and was found to be resistant to sulfathiazole.

The patient ran a septic downhill course, death occuring on the 50th day of illness. Permission for autopsy was refused.

These cases of *S. viridans* pneumonia demonstrate certain features in common as seen from Table 1. The lesion was lobar with a tendency to spread to involve more than one lobe. This was demonstrated by roentgenograms in the 4 cases where Roentgen rays were taken. A prominent symptom was intense pleural pain. Pleural effusion occurred in 4 of the 5 cases. The fluid was thin and yellow with a predominance of polynuclear leukocytes; and in none of them did it become purulent (empyema). In all 4 cases *S. viridans* was found in pure culture in the fluid. The severity of the clinical course is indicated by the fact that 4 of the 5 patients died. Death occurred on the 8th, 26th, 26th and 50th day respectively. The one patient who survived, recovered

TABLE 1.—CLINICAL AND LABORATORY FINDINGS IN A SERIES OF STREPTOCOCCUS VIRIDANS PNEUMONIAS

Case	Age	Sex	History	Chest pains	Chest fluid or lung juice	Sputum	Organism found in sputum	Bacteremia	W.B.C. (thous.)	Roentgen-ray findings	Clinical course	Outcome	Therapy	Remarks
1. W. H. White	82	M	Chest cold for 3 wks.	Sev.	Strep. v.	Thick, gray	Strep. v.	Strep. v. heavy growth	16	None	Severe, pn. entire rt. lung with effusion; death on 8th day	D	None	Organism in pure culture from sputum, chest fluid and blood
2. W. M. P. Negro	20	F	2 days following tooth extraction developed cough and pain	Sev.	Strep. v.	Mucopurulent, not foul, occasionally bloody	Strep. v., pnc. XXIX	No	13-6	Pn. RLL with effusion	Very severe, prolonged, fatal on 26th day; pleural effusion	D	Sfp., serum	No effect from sfp. therapy
3. M. T. White	59	M	2 weeks "cold," chills and fever	Mod.	Strep. v.	Thick and mucoid	Strep. v. pnc. XIII	No	15	Consolidation, entire right lung with effusion	Severe, died on 26th day, migrating pn.	D	Sfp., serum	Autopsy
4. S. L. Chinese	52	M	Cough, fever and chills, 3 days	Sev.	Strep. v.	Thick, mucoid; at times bloody	Strep. v., pnc. II, IX, XXIX	Strep. v.	21-6	Pn. RLL, RML with effusion; later the Roentgen rays showed pn. LUL	Severe, prolonged, and extremely exhausting, migrating pn	R	Sfp., smt., pn II serum	Prolonged, severe course; recovery not due to therapy
5. P. S. White	59	M	Chills, fever, pain	Mod.	None	Thick, mucoid	Pnc. III, XII, XXXII	Strep. v.	16	Consolidation, both lower lobes	Severe; history of pneumoconiosis; died on 50th day	D	St.	Organism tested, found resistant to st.

Abbreviations: M, male; F, female; Strep. v., *Streptococcus viridans;* Pn., pneumonia; Pnc., pneumococcus; R, recovered; D, died; RLL, right lower lobe; LUL, left upper lobe, etc.; Sfp., sulfapyridine; Smt., sulfamethylthiazole; St., sulfathiazole; Sev., severe; Mod., moderate.

only after a prolonged and exhausting illness lasting approximately 2 months.

Because of the well-known affinity of the *S. viridans* for the heart valves, careful attention was paid to the examination of the heart. No murmurs, embolic phenomena or other evidences of endocarditis were noted in any of these cases, nor were valvular lesions present in the bacteremic patient who came to autopsy.

The sputum was thick and mucoid, sometimes mucopurulent. The prune-juice sputum seen commonly in pneumococcic pneumonia was not observed, although in one of the cases the sputum was bloody for a few days. The *S. viridans* was the predominating organism in the sputum of 4 of the patients, though in 3 of them it was associated with pneumococci. Leukocytosis of a moderate degree was present in all the patients during the acute phases of the illness.

Bacteremia occurred in 3 of the patients, of whom 1 recovered. Both of the non-bacteremic patients died. There does not seem to be any evident relationship between the occurrence of bacteremia and the outcome of the disease.

Analysis of the data in Table 1 shows that in all these cases the *S. viridans* was cultured from one or more of the following sources: the blood, the chest fluid or the lung juice. The mere finding of the organism in the sputum even in pure culture is insufficient proof of the diagnosis, though it should stimulate the search for the organism in the blood, pleural fluid and lung juice, particularly in atypical pneumonias.

It is obvious that the usual rapid method of sputum typing by the capsule swelling phenomenon will fail to disclose the *S. viridans*. Sputum culture on blood agar plates is essential for its isolation. Mouse inoculation followed later by plating of the peritoneal exudate of the mouse is also a satisfactory method. The bile solubility test should be performed routinely to differentiate pneumococcus from streptococcus colonies. This was done in each case of this series.

One of the circumstances that should raise suspicion of the possibility that the *S. viridans* is present either as a primary or secondary invader is the failure of the patient to respond to chemotherapy. Sulfapyridine was used in 3 cases, sulfathiazole and sulfamethylthiazole were used in 1 case each with no perceptible influence on the disease.

In one of the cases the organism was tested for us by Dr. W. D. Sutliff for sulfathiazole resistance. It was found to be resistant. This is suggestive and certainly fits in with the clinical lack of response to chemotherapy.

Literature. Bullowa[1] noted 118 cases where the *S. viridans* was recovered from the sputum among 4416 typed cases of pneumonia in adults. In none of these cases was the organism found in the lung juice or the blood. The mortality rate was 13.5%. Bullowa concluded however, that in most of these cases it was difficult to assess the etiologic significance of the organism recovered. The non-hemolytic streptococcus may have been responsible for the disease or may have been an incidental finding in pneumonia due to another organism. In our cases this element of doubt was greatly reduced by the recovery of the organism from the lung juice or the blood or from both sources.

Cecil[2] in 1918 reported an epidemic of streptococcic pneumonia and empyema occurring at Camp Upton. Sixty-four of the cases were attributed to non-hemolytic streptococci. However, in a personal communication to the authors, Cecil pointed out that in these patients the diagnosis was not confirmed by isolation of the organism from the pleural fluid or blood. It should be borne in mind that when this study was made, a pandemic of streptococcic pneumonia complicating influenza swept the country.

The divergence of opinion regarding the pathogenicity of the *S. viridans* is illustrated by Reimann's statement[6] that this organism is definitely associated with only one disease, subacute bacterial endocarditis. Menton[4] in 1932 found the *S. salivarius* in the lungs and blood at autopsy in several cases of fulminating bronchopneumonia in children. Gerhartz[3] in 1934 described 3 cases of pneumonia due to the enterococcus with insidious onset, migrating pneumonia and resolution by lysis.

Senerchia and Livengood[8] reported 8 cases of pneumonia which they attributed to the *S. viridans*. Two of their patients died and the remainder had a prolonged and exhausting illness. The clinical course of these cases lends support, in view of our experience, to the belief that they were due to *S. viridans*, although the organism was recovered only from the sputum in 7 of the cases.

Reimann[7] reported a series of atypical pneumonias, from 2 of which he was able to isolate a virus. The finding of the *S. viridans* in the sputum, pleural fluid and blood of our cases distinguishes them from Reimann's group. Moreover, the cases described by Reimann had a diffuse bronchopneumonia with rarely any evidence of consolidation, while our patients showed consolidation both on physical examination and by roentgenogram.

Summary. 1. We have reported 5 cases of atypical pneumonia in which the *S. viridans* appears to have been the etiologic agent, since it was recovered from sources other than the sputum.

2. An analysis of these cases presents the following features which should suggest the diagnosis of pneumonia due to *S. viridans:* (*a*) a prolonged severe course (with a high mortality rate); (*b*) severe pleuritic reaction with serous effusion; (*c*) failure of response to chemotherapy.

3. Atypical pneumonia not responding to chemotherapy may be caused by the *S. viridans*. A careful search for this organism should be instituted from the blood and pleural fluid as well as the sputum.

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PNEUMOCOCCIC PNEUMONIA: THE SELECTION AND CONTROL OF SERUM AND CHEMOTHERAPY BY SPUTUM EXAMINATION*

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During the past few years we have been utilizing Wright stained smears of rusty sputum from patients with pneumonia as an index of prognosis and as a guide to therapy. The outcome of the pneumonia could be predicted more accurately by the number of pneumococci in the sputum than by any of the usual prognostic criteria such as type, bacteremia, leukocyte count, duration of the disease, age, and the degree of involvement.[5,9] The fatality rate was uniformly low in patients with less than 30 pneumococci per field and uniformly high in those with sputum counts over 30 irrespective of the above factors. Furthermore, the specific response of individual patients to serum and sulfonamides could be readily followed by the examination of sputum at intervals during the course of the disease. While the end result of both of these forms of therapy is a reduction in the number of organisms in the sputum and lungs, this is accomplished in a different manner by each of the therapeutic agents. Adequate serum in moderately ill patients brings about a prompt agglutination of the pneumococci in the sputum within 6 to 12 hours, which is usually followed by phagocytosis and a gradual reduction in the number of organisms over a period of several days.[1,2,3] When large numbers of pneumococci are present, serum is inefficient and actual multiplication may occur despite the presence of excess antibody in the blood.[1,3,7] The sulfonamides, on the other hand, exert a direct bacteriostatic action which is manifested by a reduction in the number of pneumococci within 12 to 36 hours. A striking effect is obtained in the sputum regardless of the number originally present[3,4,7] except in the rare instances where drug fastness develops.[3,4,6] The marked superiority of sulfapyridine, sulfathiazole, and sulfadiazine over serum or sulfanilamide may be best demonstrated in the more severely ill patients with sputum counts exceeding 30 per field.[9]

On the basis of the foregoing observations, the microscopic examination of sputum would appear to be a practical method of individualizing therapy in pneumococcic pneumonia. Thus the mild cases could be differentiated from the severe ones by sputum counts and the dosage of serum or drugs controlled by following the effects in the sputum. Preliminary data supporting this premise have already been presented

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in a therapeutic experiment involving 270 cases of pneumococcic pneumonia.[8] There were no deaths in 118 patients with sputum counts below 10 for whom supportive or serum therapy was selected; whereas, the fatality rate was 16% in 138 cases with sputum counts above 10 despite modern chemotherapy. The object of the present communication is to present additional data concerning the sputum count as a means of selecting therapy and also to evaluate it as a method of controlling the dosage of both serum and the sulfonamides in individual patients with pneumonia.

Method. Specimens of rusty sputum were obtained on admission to the hospital, and the number of pneumococci per field was determined by the method previously described.[5,9] The diagnosis of pneumonia was confirmed by roentgenogram in each case. Therapy was then initiated in accordance with the sputum count as outlined in Table 1. Subsequent specimens of sputum were obtained at intervals of 12 hours or less in order to determine whether or not a therapeutic effect had occurred. When the counts decreased, the dosage was reduced as indicated in Table 1. If the number of pneumococci increased beyond the limits of the range in which the patient was originally classed, the therapy was modified to conform with that established for the new zone. The schedule in Table 1 was adhered to as strictly as possible except in those cases with original sputum counts exceeding 50 per field. The fatality was so high in this group that we did not dare risk a relapse by discontinuing therapy too soon. The dosage of 0.5 gm. every 4 hours was, therefore, continued for 1 or 2 days after a full drug effect had been observed in the sputum.

TABLE 1.—THE SELECTION AND CONTROL OF THERAPY BY SPUTUM COUNTS

Pneumococci per O. I. F.	Duration of disease (hrs.)	Sputum clumping	Therapy	Dosage
10 or less	Less than 96 More than 96	+ + or −	Supportive	
10 or less	Less than 96	−	Serum	5000 to 50,000 units.
11 to 20	Any	+ or −	Sulfonamide, small doses	Gm. 2 stat., gm. 0.5 q. 4 h. around clock. Discontinue when count reduced to occasional pneumococcus per field.
21 to 35	Any	+ or −	Sulfonamide, mod. doses	Gm. 4 stat., gm. 1 q. 4 h. around clock. When sputum count reaches 10 or less, reduce drug to gm. 0.5 q. 4 h. Discontinue as above.
36 to 50	Any	+ or −	Sodium salt of sulfonamide, large doses	Gm. 4 i.v. stat., gm. 2 i.v. q. 2 h. for 2 doses. Then give gm. 2 q. 4 h. around clock. When sputum count reaches 25, reduce drug to gm. 1 q. 4 h. For additional dosage see sputum group 21 to 35.
More than 50	Any	+ or −	Sodium salt of sulfonamide Serum*	Dosage as in sputum group 36 to 50. Minimum of 300,000 units.

* Serum was omitted in the latter cases of this series for reasons which will be discussed.

Results in Cases with Initial Sputum Counts of 10 or Less. When the sputum count on admission did not exceed 10 pneumococci per field, the cases were classed as mild pneumonias and either serum or supportive therapy was instituted depending upon the duration of the disease and the immune status of the patient. Supportive treatment was selected for (*a*) those whose sputums contained agglutinated

pneumococci prior to the 4th day of the disease thus indicating the development of an active immunity, and (*b*) for those who had been ill longer than 4 days on the assumption that immune bodies would appear in time to dispose of the small number of pneumococci present.* On the basis of the foregoing criteria, 108 patients were started on supportive measures only (Table 2). Nine per cent had positive blood cultures, 16% had leukocyte counts under 10,000 during the acute stages, and 18% showed involvement of more than 1 lobe. The prognosis as based on the initial sputum count was erroneous in 3 cases which proved fatal. The number of pneumococci in the sputum increased in 2 of these, but the institution of chemotherapy failed to prevent death. The fatal outcome was due in part to complicating pericarditis in 1 case and to uremia in the other. In the third patient who died, the pneumonia gradually extended from 1 to 4 lobes despite the fact that the sputum count remained below 10 per field throughout his illness. All 3 cases showed relatively few pneumococci in the lungs at necropsy. In 9 additional cases, the pneumococci increased sufficiently to bring the count within the 11 to 20 range and the appropriate chemotherapy was accordingly instituted, following which a prompt fall in sputum count and an uneventful recovery occurred. The prognosis as based upon sputum counts proved correct in 96 of the 108 cases for whom supportive therapy was originally selected since all recovered without specific treatment. Evidence of active immunity as indicated by spontaneous agglutination of the pneumococci in the sputum was obtained in 72% of the patients. The fact that approximately 90% of the patients made the anticipated recovery without specific treatment proves the validity of the criteria originally set forth in the selection of cases.

When the illness was less than 96 hours in duration and the number of pneumococci in the sputum did not exceed an average of 10 per field, serum was given in doses just sufficient to induce agglutination. Serum therapy was accordingly selected for a total of 114 cases fulfilling the above criteria in order to determine whether or not such small doses were adequate for recovery (Table 2). Eighteen per cent of the cases had bacteremia, 7% had leukopenia, and 20% showed consolidation of more than 1 lobe. Subsequent specimens were examined at 6 to 12-hour intervals during the course of the disease and no additional therapy was given as long as clumping was maintained and the count did not rise above 10. Serum in this dosage proved inadequate in 9 cases. In 7 of these, including 1 fatality, the sputum count increased above 10 per field and chemotherapy was given. In 2 of the 9 patients the sputum count remained below 10, but pericarditis developed; one survived following chemotherapy, but the other expired. The remaining 105 of the original 114 cases recovered with serum therapy alone. Agglutination of the pneumococci in the sputum was induced and maintained in 95% of the patients in this group; so few organisms were

* The spontaneous clumping of pneumococci in the sputum is frequently associated with the appearance of agglutinins in the circulating blood (unpublished data).

present in the other 5% that clumps could not be demonstrated.* The average total dose of serum administered to each patient was 35,000 units, an amount usually considered inadequate by the majority of investigators. In fact, as little as 2,000 units produced prompt agglutination in some cases. The average dose for bacteremics was only 45,000 units and a minimum of 10,000 sufficed in several instances. These data show that small doses of serum as controlled by sputum examinations were adequate for the recovery of over 90% of the patients who satisfied the criteria set forth in the selection of cases.

TABLE 2.—SUMMARY OF CASES

Sputum count	Original therapy	Dosage	Total cases	Per cent				Therapy			
				Bacteremia	Leukopenia	Multiple lobes	Fatality	Unchanged		Changed	
								Cases	Deaths	Cases	Deaths
10 or less	Supportive		108	9	16	18	3	97	1	11	2
	Serum	35,000 U	114	18	7	20	2	105	0	9	2
	Sulfonamides	Routine NC	118	12	11	15	1	118	1		
11 to 20	Sulfonamides	Small C	102	33	18	42	6	87	4	15	2
	Sulfonamides	Routine NC	67	33	9	31	9	67	6		
21 to 35	Sulfonamides	Moderate C	81	33	17	48	2	81	2		
36 to 50	Sulfonamides	Large C	34	68	41	76	9	34	3		
Over 50	Combined	Large C	27	81	63	85	56	27	15		
	Sulfonamides	All*	43	70	67	84	58	43	25		

NC = Not Controlled. C = Controlled.
* 19 cases received Routine NC and 24 received Large C.
Total cases: per cent by type: I, 26; II, 14; IV and V, 12; VII, 21; VIII, 12; others, 15.

The results in the above cases treated with serum and supportive measures compare favorably with those obtained in a group of 118 unselected cases with initial sputum counts of 10 or less who received routine chemotherapy (Table 2). This consisted of an initial dose of 4 gm. of sulfapyridine, sulfathiazole, or sulfadiazine, followed by 1 gm. every 4 hours thereafter until an adequate clinical response was observed. The incidence of bacteremia, leukopenia and multiple lobe involvement in the sulfonamide controls corresponded closely to the averages for the other two groups (Table 2), but the fatality rate and number of complications were not significantly reduced. Defervescence occurred within 48 hours after treatment in 52% of the cases receiving supportive therapy, in 64% of those given small doses of serum, and in 70% of those receiving routine doses of sulfonamides (Table 3).

* The agglutination of pneumococci in the sputum following serum therapy has been described previously together with preliminary data on the control of dosage.[1,2,7] We considered that an appropriate response had been obtained when distinct clumps of pneumococci appeared even though all organisms were not agglutinated. As long as clumping was maintained, no additional serum was given. One dose of serum was sufficient in 81 cases; two were necessary in 21; and three or more were required in 4 patients.

TABLE 3.—CLINICAL RESPONSE TO THERAPY

Sputum count	Therapy	Dosage	Total cases	Fatality (%)	Treatment (average)		Hours to defervescence (in %)			Complications (%)	Relapses
					Dose (gm.)	Days	48 or less	49 to 96	Over 96		
10 or less	Supportive		97	1	..	..	52	28	20	4	
	Serum	35,000 U	105	0	..	..	64	20	16	4	4
	Sulfonamides	Routine NC*	118	1	27	4.5	70	15	15	3	4
11 to 20	Sulfonamides	Small C	87	5	13	3.5	47	16	37	14	9
	Sulfonamides	Routine NC	67	9	31	5.2	59	18	23	6	1
21 to 35	Sulfonamides	Moderate C	81	2	21	4.0	35	26	39	10	3
36 to 50	Sulfonamides	Large C	34	9	34	4.7	27	15	58	28	1
Over 50	Combined†	Large C	27	56	45	5.8					
	Sulfonamides	Routine NC	19	79	32	6.5	17	10	73	27	
	Sulfonamides	Large C	24	42	52	7.2					

C = Controlled. NC = Not Controlled.
* Therapy not selected by sputum count.
† An average of 410,000 units of serum was given to each patient who survived.

Results in Cases with Sputum Counts Between 11 and 35. If the initial sputum count exceeded 10 per field, chemotherapy was deemed necessary regardless of the immune state or duration of the disease. For cases within the 11 to 20 range, either sulfapyridine, sulfathiazole or sulfadiazine were given in an initial dose of 2 gm. followed by 0.5 gm. every 4 hours to determine whether such small doses were sufficient to reduce the number of pneumococci in the sputum and to bring about a recovery. A total of 102 cases were treated in this manner (Table 2). Thirty-three per cent had bacteremia, 18% had leukopenia, and 42% showed involvement of more than 1 lobe. There were 6 deaths in the series, 2 of which were due to uncomplicated pneumonia. A third patient died in delirium tremens shortly after the administration of the initial dose; another expired with a Type III pneumonia after recovery from the original Type VII infection; a fifth died in uremia; and the last developed meningitis and expired despite large doses of serum and sulfapyridine. The response in the sputum was unsatisfactory in 13 other cases, but each survived after the dosage of sulfonamide had been increased. Nine relapses occurred in the remaining 84 patients because of too rapid removal of drug, but all recovered without modification of the original plan of treatment. These patients, who constituted 82% of the entire group, received an average of only 13 gm. of sulfonamides over a period of 3.5 days (Table 3). Included among the 84 patients who recovered on such small doses were 23 cases with bacteremia, 14 with leukopenia and 32 with involvement of more than 1 lobe.

Sixty-seven additional patients with sputum counts in the 11 to 20 range and a comparable incidence of bacteremia and multiple lobe involvement who were given routine doses of chemotherapy have been

included as controls for the above group (Tables 2 and 3). The survivors received an average total dose of 31 gm. of drug over a period of 5.2 days. In spite of the fact that the initial and subsequent doses were twice as great as in the group where therapy was controlled by sputum findings, the fatality rate and the duration of the disease were not significantly altered. The incidence of complications and relapses, however, was appreciably lower in the group receiving routine chemotherapy. These data show that over 80% of the cases classified as moderately ill on the basis of an initial sputum count between 11 and 20 will recover on half the customary dose of sulfonamides.

When the admission sputum count ranged between 21 and 35, chemotherapy was given in an initial dose of 4 gm. followed by 1 gm. every 4 hours. As soon as the count fell below 10 per field the dosage was reduced by half and the drug was discontinued when a full effect was observed (Table 1). As a consequence of the control of dosage by sputum examination the average total drug given to the 81 patients treated in this manner was 21 gm. over a period of 4 days. Although the disease was somewhat more severe than in the above group given routine chemotherapy as shown by the higher sputum count and the greater incidence of multiple lobe involvement and leukopenia, the fatality nevertheless was very low, amounting to only 2% (Table 2).* The clinical response, however, was slower, defervescence occurring within 48 hours in only 35% of the 79 cases which recovered in contrast to 59% among those treated routinely (Table 3). These data show that both the sulfonamide dosage and the duration of therapy may be safely controlled by sputum examination and that excellent end results may be obtained with less than the customary amount of chemotherapy.

Results in Cases with Sputum Counts Over 35. Those patients with sputum counts between 36 and 50 per field were classed as severely ill and were, therefore, considered as candidates for the sodium salts of the sulfonamides in double the routine dosage. They received 4 gm. intravenously on admission followed by 4 gm. within the next 4 hours and 2 gm. orally every 4 hours thereafter until an effect was observed in the sputum. The characterization of the pneumonic process as severe was also borne out by the fact that 68% had bacteremia, 41% showed leukopenia, and 76% had 2 or more lobes involved.† The fatality rate of only 9% in the presence of such a high incidence of unfavorable prognostic factors may be ascribed to the intensive chemotherapy, as will be more clearly shown in the group with sputum counts exceeding 50. The average total dosage of sulfonamide was 34 gm., approximately half of which was administered during the first 24 hours, the remainder given in diminishing doses during the next 3.7 days. Defervescence occurred within 48 hours in only 27% of the cases. The longer course was in part attributable to the fact that 28% had complications (Table 3).

The last group of patients with sputum counts over 50 per field were classed as overwhelmed pneumonias and, therefore, received

* A decrease in the number of pneumococci in the sputum occurred in 94% of the cases.
† A therapeutic response was observed in the sputums of 92% of the cases.

intensive therapy (Table 2). Early in the study it was felt that large doses of serum coupled with intravenous sulfonamides offered the greatest hope for recovery in this group of cases. The fatality rate, however, among 27 patients treated in this manner was 56%. The survivors received an average dose of 410,000 units of serum plus 45 gm. of drug over a period of 5.8 days.* Inasmuch as cases of this severity offered an excellent means of determining whether supplementary serum contributed significantly towards the recovery, we accordingly treated a group of 43 comparable cases with sulfonamides exclusively, with the resultant fatality of 58%. Among this group of 43 patients there were 19 who received the routine dosage of 4 gm. of sulfonamide on admission and 1 gm. every 4 hours thereafter. In those who recovered, the average total dose was 32 gm. over a period of 6.5 days. These cases were contrasted with a group of 24 others in which the sodium salt was administered intravenously in large doses as described above. Those that recovered received an average total of 52 gm. of drug over a period of 7.2 days without serious toxic reactions. The fatality in the latter group was 42% in contrast to 79% in the former given routine doses (Tables 2 and 3).† These data support our contention that the overwhelmed cases may be detected by means of the sputum count. Furthermore, they show that supplementary serum contributes insignificantly towards recovery; that massive doses of sulfonamide intravenously offer a greater chance of survival; and finally (Table 3), a clinical response within 48 hours is the exception rather than the rule in such severely ill patients.

Discussion. The determination of the average number of pneumococci in Wright stained smears of rusty sputum has proved to be a simple and reliable method for the selection of therapy in pneumococcic pneumonia. The admission sputum count was of considerable aid in differentiating the mild and moderately ill from the critically ill patients. Although it was shown that over 90% of the mild cases recovered with minimal doses of serum or with supportive treatment only, we believe that these patients would have responded more promptly to small amounts of sulfapyridine, sulfathiazole or sulfadiazine and with less danger of extension or relapse. The chief value of the admission sputum count lies in the fact that it provides a means for the prompt recognition of critically ill patients who should have immediate and intensive therapy. Our original premise that large doses of serum in conjunction with the sulfonamides would offer more chance of recovery than chemotherapy alone was not borne out by the results. Although the effects of both agents were demonstrable in the sputum, and although the eventual reduction in the number of pneumococci was accomplished by two entirely different mechanisms, the data showed that the beneficial results with combined treatment were primarily due to the sulfonamides and not to the serum.‡ In addition,

* An effect from serum was observed in 45% and from chemotherapy in 52% of the cases.

† An effect from therapy was noted in the sputums of 68% and 47% respectively.

‡ Early in the study 8 cases with sputum counts exceeding 50 were treated with serum alone and all expired.

the clearly demonstrated superiority of intravenous chemotherapy in large doses over oral drug in routine doses again emphasizes the importance of adequate treatment in the critically ill patients with sputum counts exceeding 50. Since a high fatality rate still prevails in this group and because no serious toxic manifestations resulted from the doses used, the desirability of even larger doses during the first 48 hours should be seriously considered. In our opinion the major problems are first, to keep the patients alive long enough for the sulfonamides to exert an effect, and second, to carry them through the complications that so frequently develop. Thus, among the fulminating cases with high sputum counts a total of 25 of the 40 deaths occurred within the first 24 hours after therapy had been started. Ten of the 15 which survived more than 24 hours showed a maximal reduction in the number of pneumococci in the sputum and in the lungs at necropsy. Purulent complications were responsible for 6 of the 10 deaths and serious associated diseases were important contributing factors in the other 4 cases. The remaining 5 deaths included 4 cases in which the pneumococci had become resistant to the sulfonamides and 1 patient who expired within 36 hours after therapy had been instituted. In view of the fact that intravenous chemotherapy in the doses used reduced the fatality rate from 79 to 42%, it is possible even larger doses might be more effective when the sputum count exceeds 50 per field.

Supplementary serum has been generally advocated for patients who fail to respond to drugs within the first 48 hours after therapy has been instituted. Our data are at variance with this concept since it has been shown that even under optimal conditions for recovery (sputum counts below 10) defervescence occurred within 48 hours in only 70% of the cases treated with sulfonamides. Furthermore, the clinical response was markedly delayed in the overwhelmed cases, where it was found that less than 20% showed a defervescence within 48 hours after treatment with massive doses of sulfonamides often supplemented by serum. As a general rule, a full bacteriostatic effect from chemotherapy was demonstrable in the sputum and lungs[7] of the vast majority of patients who lived more than 48 hours after treatment had been instituted. A failure to obtain a clinical response after 48 hours of chemotherapy was attributable either to the overwhelming nature of the primary disease, to complications, occasionally to drug resistance, or to other factors which are not at present understood. Relatively few cases were seen in which the pneumococci were refractory to the bacteriostatic action of the sulfonamides. Among the total 694 cases studied there were only 12 (2%) who were classified as resistant either because the drug failed to reduce the number of pneumococci or because the organisms, after an initial decrease, returned to the sputum while the drug was being administered.[3,4,6] As a result of these observations we believe that the use of serum should be limited to the few cases in which drug resistance is demonstrable.

The reliability of the sputum as a method for the control of serum dosage is evident from the data presented. During the period when

serum was the only available specific remedy for pneumonia, the standard dosage was based largely on clinical experience. In an attempt to prevent failures in the seriously ill patients, there was a trend toward a gradual increase in the recommended dose of serum. The utilization of the sputum as a means of controlling serum dosage has shown that in more than 90% of properly selected cases, an average of 35,000 units was sufficient to effect a recovery. The Francis test as a method of judging serum dosage has been disappointing in our hands. Over 60% of the cases gave false positive skin reactions on admission despite the fact that polysaccharide from 4 different sources was tried. We also noted that the skin test remained negative in many patients who responded well to minimal doses of serum. When excessive doses were used, a positive test was elicited.

The moderate to mildly ill patients with sputum counts under 35 who constituted 85% of the total admissions have hitherto received larger amounts of sulfonamide over a longer period of time than is actually necessary. By reducing the dosage as the number of pneumococci decreased and by withdrawing the drug after a full effect was evident in the sputum, satisfactory results were obtained with a total dose of 10 to 25 gm. administered over a period of 3.5 to 4.5 days. In these cases it was found that minimal effective blood concentrations were between 3 and 4 mg. per 100 cc. for sulfapyridine and sulfadiazine and between 1 and 2 mg. per 100 cc. for sulfathiazole. Although the initial small dosage did not appear to encourage the development of drug resistance, the incidence of relapses and complications was higher than in a comparable group of cases receiving routine doses (Table 3). For the above reasons we believe that the small dosage scheme should be so modified that larger amounts of drug are given during the first 24 to 48 hours and the subsequent dosage controlled according to the sputum response. By this method the maximum therapeutic efficiency of the sulfonamide drugs would be insured, but their toxic and sensitizing effects[10] would be minimized.

Summary. The treatment of pneumococcic pneumonia was individualized by dividing the cases into 3 major prognosis groups according to the number of pneumococci in Wright stained smears of rusty sputum. The cases in the first group represented approximately 50% of the total admissions and were classed as relatively mild on the basis of sputum counts of 10 or less during the course of the disease. Over 95% of these recovered with supportive therapy, with small doses of serum or with sulfonamides. Although the very low fatality rate of 2% was not appreciably altered by sulfonamides, the pneumococci were more effectively prevented from multiplying and a more rapid defervescence was induced. The patients in the second group represented approximately 35% of the total admissions and were classed as moderately ill on the basis of sputum counts between 11 and 35 per field. By decreasing the dosage when a therapeutic response was elicited in the sputum, the total amount of sulfonamide administered was significantly reduced without affecting the final fatality rate. The last group with sputum counts over 35 included only 15% of the total

cases, but was responsible for 70% of the deaths. The sodium salts of the sulfonamides in large doses intravenously were the most effective therapeutic agents. Supplementary serum proved to be of no additional value in the most severe cases with sputum counts exceeding 50 per field. From this study it was concluded that the initial and subsequent examination of sputum can be effectively utilized as a method for the selection and control of therapy in pneumococcic pneumonia.

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XANTHOMATOSIS—HAND-SCHÜLLER-CHRISTIAN TYPE: REPORT OF A CASE WITH PULMONARY FIBROSIS

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This disease was first described by Schüller* in 1915 and elaborated upon by Christian in 1919 and Rowland in 1928. It has since been accepted as a distinct clinical entity, as is evidenced by the frequent reports of cases of it in the literature. The presence of (1) map-like defects of the skull, (2) exophthalmos, and (3) signs of hypopituitarism (diabetes insipidus and dwarfism) have been generally accepted as the triad necessary to the making of a conclusive diagnosis. Experience, however, has shown that such actually is not the case, since only one or two of the clinical signs may be present. It has been found also that involvement may occur in any part of the reticulo-endothelial system in the body. Such clinical signs as lymphadenopathy, pulmonary fibrosis, hyperpyrexia, hepatomegaly and splenomegaly, involvement of the long bones and icterus may be found.

The etiology of the disease remains obscure, although it is thought to be due probably to a disturbance in lipoid metabolism, especially of cholesterol metabolism, and of the cholesterol esters, possibly in the cells of the reticulo-endothelial system. Thannhauser, in his recent (1940) complete monograph referred to this disease as a primary essential xanthomatosis of the normal cholesteremic type. However, the histologic appearance of some of the tumor suggests very strongly to some pathologists that the disease may be an infectious type of granuloma.

* The first clinical description of this condition was made by Alfred Hand (Pr. Phila. Path. Soc., 1895), who recognized the main triad but, like the other early investigators, has incorrect ideas as to its etiology. Editor.

The following case is presented as one of xanthomatosis (Hand-Schüller-Christian's type) with the usual osseous lesions and also extensive pulmonary fibrosis. Several interesting features are presented, including the results of Roentgen therapy.

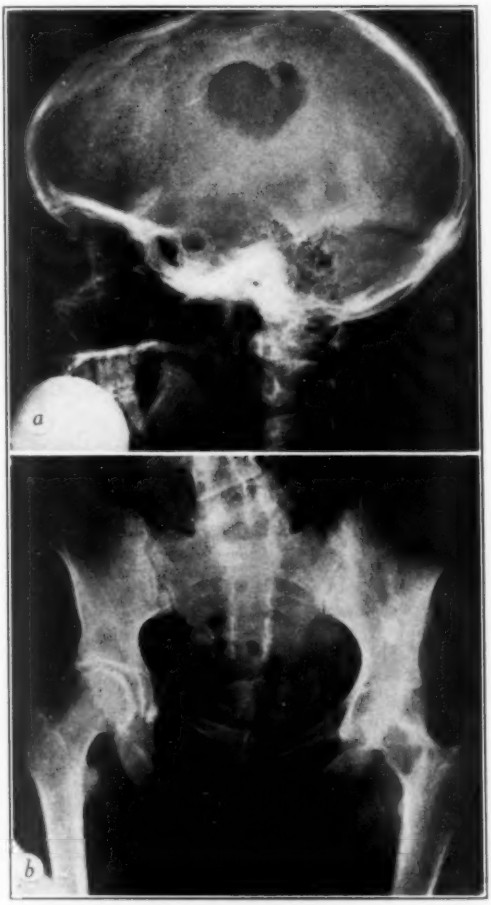

FIG. 1.—*a*, Parietal bone lesions before Roentgen therapy; *b*, lesion in the neck of the left femur before Roentgen therapy.

Report of a Case. The patient, a 29 year old single woman, entered the Mayo Clinic on January 5, 1942. At the age of 7 years she had had poliomyelitis which resulted in partial paralysis of the right arm and left leg and moderate scoliosis of the thoracic part of the spinal column. In July, 1938, pain and stiffness developed in the left hip, persisted for 2 weeks, and then subsided. Similar symptoms returned 6 months later and were present for 2 weeks. In March, 1941, she noted intermittent twinges of pain over the right parietal portion of the skull, followed in 6 months by a palpable swelling in this region. This swelling persisted and seemed to have become somewhat larger since it had been first noted. In November, 1941, a dull aching pain developed in the left hip, associated with soreness on motion. This pain became worse and prompted the patient's visit to the clinic.

Physical examination revealed a thin woman with moderate dorsal kyphosis and moderate atrophy of the muscles of the right arm and left leg. Over the right midparietal region of the skull was a soft, raised zone with discrete borders about 6 cm. in diameter which was tender on palpation. Results of thoracic examination were negative. The heart rhythm was regular, sounds were normal, and the rate was 110. The blood pressure was 120, systolic, and 85, diastolic, expressed in millimeters of mercury. The right kidney was palpable. Over the greater trochanteric region of the left thigh there was tenderness to palpation, and motion of the left hip was mildly limited because of pain. The patient weighed 95 pounds (about 43 kg.).

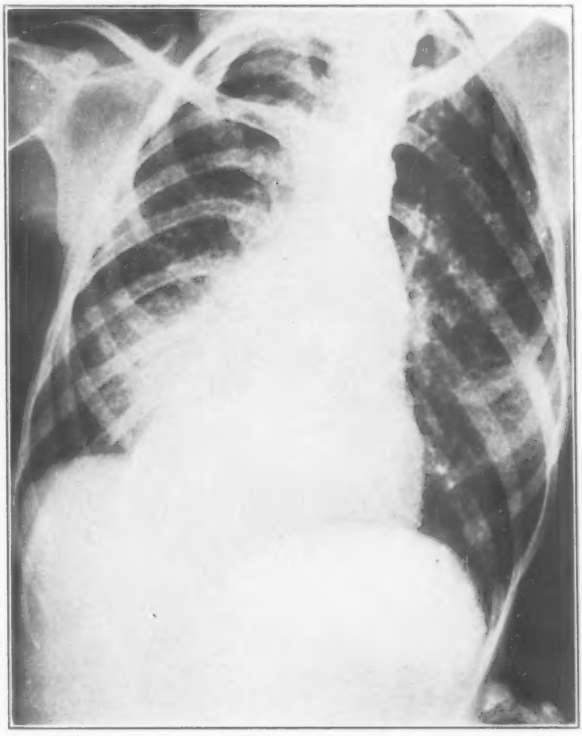

FIG. 2.—Pulmonary lesion before Roentgen therapy.

Examination of the blood revealed a value for hemoglobin of 11 gm. per 100 cc. and an erythrocyte count of 4,810,000. The leukocyte count was 8600, with a differential count of 23% lymphocytes, 12% monocytes, 62% neutrophils, 2% eosinophils and 1% basophils. Examination of blood smear demonstrated mild hypochromic anemia. Results of serologic examination for syphilis were negative. Roentgenograms of the skull disclosed an irregular zone of destruction of bone in the right parietal region (Fig. 1*a*). In the neck of the left femur was a similar defect (Fig. 1*b*). A roentgenogram of the thorax disclosed bilateral extensive fibrosis (Fig. 2). Results of roentgenograms of the rest of the long bones and hands were negative. Results of blood lipoid studies were as follows: cholesterol 177, cholesterol esters 120, fatty acids 327, and total lipoids 501 mg. per 100 cc. of plasma. The value for blood calcium was 10.2 mg., for phosphorus, 3.9 mg., and for phosphatase 1.6 units, per 100 cc. of serum. The value for plasma proteins was 7.9 gm. per 100 cc., with a ratio

of 1.4:1. The sedimentation rate was 44 mm. per hour. The reaction to the Mantoux test was negative in the second-strength solution. The basal metabolic rate was +15. On January 10, 1942, the extradural swelling on the right side of the skull was removed and the pathologic report was: "Hand-Schüller Christian's disease with areas of necrosis and hemorrhage." Chemical

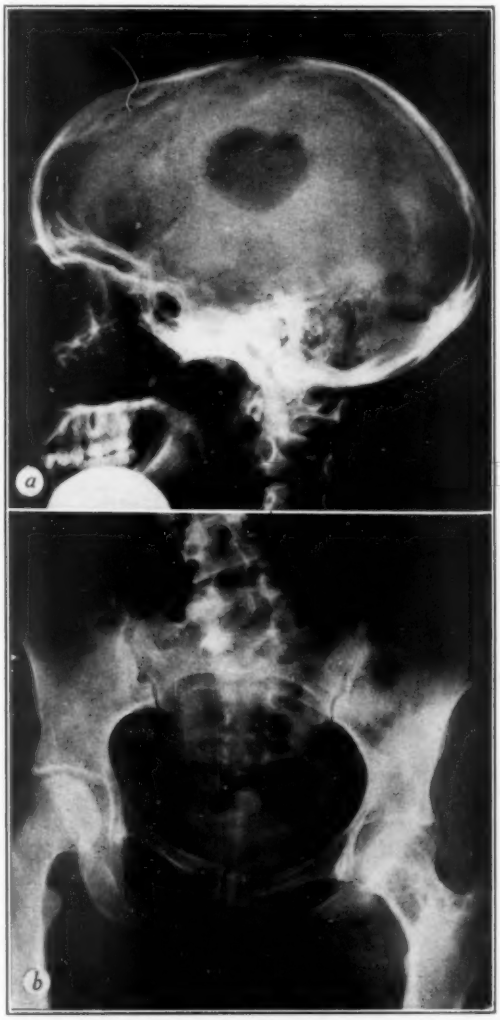

FIG. 3.—*a*, Parietal lesion after Roentgen therapy; *b*, lesion in the neck of the left femur after Roentgen therapy.

analysis of this tissue for the lipoids revealed the following: cholesterol 0.69%, cholesterol esters 0.29%, lecithin 0.42%, fatty acids 1.36%, and a total lipoid of 2.05%, of the wet weight of the tissue.

The cystic-like zones involving the calvarium and femur were the outstanding features of the case, and accounted for the symptoms of the patient. However, the finding of what appeared to be diffuse fibrosis of the lungs was

unusual. The relatively low amount of fat found in analysis of the tissue taken from the skull reveals that the granulomatous process at this stage is not rich in cholesterol and suggests that the process was relatively old. The pulmonary fibrosis likewise suggests that the disease was fairly long standing. However, in one case in which the patient was a child, recently observed by Hampton, the roentgenologic picture of the lungs changed from that of a miliary process not unlike miliary tuberculosis to that of extreme pulmonary fibrosis and emphysema, within the course of 3 months. At necropsy the alveolar walls were found to be destroyed and the interstitial tissue of the lungs was heavily infiltrated with granulomatous tissue. On the basis of Hampton's observations it seems likely that what appears to be fibrous tissue in the roentgenogram

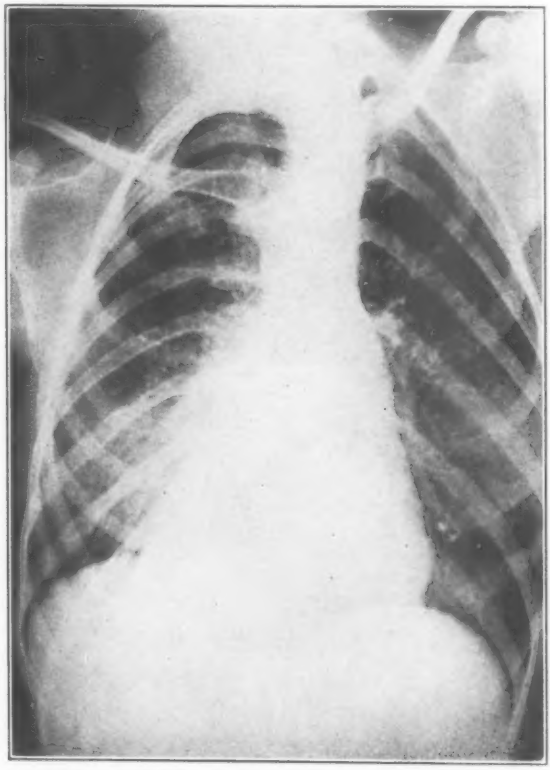

FIG. 4.—Pulmonary lesion after Roentgen therapy.

actually may be granulomatous tissue, although the ultimate result probably is fibrosis.

Roentgen therapy was begun on January 17. One treatment to the zone of involvement in the right portion of the calvarium and one anterior and one posterior field to the head of the left femur, were employed. The treatments were administered with a moderate voltage technique (130 kv. constant potential), and a total dose of approximately 270 r was utilized. Because of the possibility that the lesions in the lungs may have had a granulomatous basis, one area of treatment was given to the left lung both anteriorly and posteriorly. The treatment to the lung was carried out in this manner so that a comparison might be made between the treated and untreated side of the lung. Two addi-

tional courses of treatment were administered at monthly intervals. The last examination was done on June 17, and marked improvement was found in the osseous lesions (Fig. 3*a* and *b*). The last roentgenograms of the thorax disclosed some slight evidences of improvement (Fig. 4).

Comment. This case is unusual in that it presents pulmonary fibrosis which in the past has been seen rarely in connection with xanthomatosis. The improvement in the osseous lesions is typical of the changes seen in juvenile xanthomatosis after Roentgen therapy. In our experience Roentgen therapy in moderate doses causes a definite therapeutic response, whereas large doses call forth little or no response.

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THE ANTIBACTERIAL ACTION OF THE LACTIC ACID AND VOLATILE FATTY ACIDS OF SWEAT*

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Peck, Rosenfeld, Leifer and Bierman[3] have shown that thermal sweat may have fungistic and fungicidal properties at a pH below 7, particularly when concentrated, and that these properties depended on its content of acetic, propionic, caproic, caprylic, lactic and ascorbic acids. They also found topical applications of these acid ingredients of sweat to be valuable in the treatment of fungous infections.

One of us has been interested in the rôle of the volatile fatty acids in the inhibition, under certain circumstances, of the growth of microorganisms in the intestines of animals and man. In order to interpret these results it was necessary to study the relation of pH and of acid concentrations of the volatile fatty acids to their antibacterial action.[1a,b] These results are also applicable to sweat and should help to clarify the significance of the volatile fatty acids in this secretion, as do also certain other analogies between the situations existing in perspiration and in the intestinal contents. Some observations on sweat made from this viewpoint are here reported.

Methods. Sweat specimens were collected as follows: The subjects were encased in a rubber bag as far as their necks and seated in a heat

* The expenses of this investigation were met in part by grants made to the University of Illinois by Standard Brands, Inc.

cabinet. Incandescent lamps furnished sufficient heat to obtain from 100 to 200 cc. sweat in 20 to 30 minutes. In some cases, specimens were collected after the individual had been thoroughly scrubbed to remove any evaporated sweat from the skin surface. Other specimens were obtained without scrubbing so as to include such dried sweat. Serial specimens were also collected in order to see if there were any changes in composition during the sweating period.

Total volatile fatty acids were determined by acidification with sulphuric acid and distillation with additions of water until all volatile acid had been driven over, followed by titration, using phenolphthalein as an indicator, after the distillates had first been aërated for 15 minutes with a current of air free from carbon dioxide. Observations as to the nature of the volatile acids present were made using the method of Werkman.[4] Lactic acid was determined by the method of Friedemann and Graeser.[2] Ammonia was determined colorimetrically using Nessler's reagent. pH determinations were made with the glass electrode.

Lactic Acid in Sweat. The antibacterial action of the acids in sweat may depend in part upon their production of an inhibitory pH. For such inhibition, however, most microörganisms require a pH of below 5. In samples of heat sweat we have noted pH values as low as 5.1 but the average was 5.7. From our published studies such pH values cannot be expected to be very effective in sterilization. Effectiveness depends, however, also upon the nature of the acid The acid present in sweat in largest amounts is lactic acid (about 0.1% or about 0.01 N). Aside from the pH effect, the undissociated lactic acid also has some influence. Our observations on lactic acid indicate, however, that its molecules have a low sterilizing value (lower than that of acetic acid or any of the other volatile fatty acids) and are so few in number at the average pH of heat sweat that the lactic acid of such heat sweat could hardly have more than a mild antibacterial action with regard to most organisms. Thus lactic acid in 0.1 N solution had no inhibiting effect on the growth of *Esch. coli* when adjusted to pH 6, although at pH 5 it had some action. Of course some organisms are more susceptible than *Esch. coli* as shown in a previous paper.[1a,b] Concentration of perspiration by evaporation on the surface of the skin may, however, obviously alter the situation. Evaporation to one-tenth volume or less might bring the lactic acid normality above 0.1 and if the pH falls at the same time or remains constant at near 5 fairly effective conditions might be expected. Since lactic acid because of its larger quantity must preponderate in its effect on the pH of the sweat and because the volatile fatty acids appear to be largely formed from the lactic acid, this acid must be of primary importance.

Lactic acid appears to be secreted as such by the skin since it is present in the sweat of subjects who have been thoroughly scrubbed and since it usually decreases rather than increases in amount on incubation of sweat (Table 3). The secretion of lactic acid seems therefore to be the more fundamental process in the acid bath of the skin and determinations of lactic acid in sweat may therefore be of interest. The

necessity for a suitable pH (5.5 or lower) for its action on organisms must however never be disregarded since neutral lactates, such as sodium lactate have little if any effect.

pH of Sweat. We have found the pH of heat sweat to vary from 5.1 to 6.95 in 24 cases studied with an average pH of 5.7. The pH of the more acid of these sweats may be sufficient together with the molecular effects of lactic and fatty acids present to have some, but hardly any strong, antibacterial action. Any influence might be expected on the growth of only the more susceptible microörganisms. Ordinarily, of course, sweat is concentrated upon the surface of the skin by evaporation and since lactic acid is not volatile, a fall in pH with consequent increase in antiseptic powers might be expected. We have evaporated heat sweats at 40° C. in a current of air and found significant decreases in pH. Thus 4 sweats having pH values of 5.2, 5.3, 5.6 and 6.0 on concentrating 23 to 50 times gave values of pH 5.0 to 5.1. These changes in pH are not great, yet taken with the increase in lactic acid concentration to 0.2 N or higher may be of importance, as the growth of *Esch. coli* for example is inhibited at pH 5 by about 0.1 N lactic acid and other organisms are still more susceptible.

The influence of evaporation of sweat on the pH is not, however, a simple one since bacterial action on sweat constituents occurs simultaneously with such evaporation. Apparently the skin bacteria convert some of the lactic acid to volatile fatty acids. This might have little effect on pH. The action of organisms on organic nitrogen compounds of sweat, particularly urea, results in ammonia formation. This ammonia has a neutralizing effect on the acids. Twenty samples of heat sweat showing pH values from 5.1 to 6.5 were incubated at 37° C. for 18 hours. The resultant pH values varied from 6.25 to 8.30 and were mostly above pH 7.0. Some of the results are included in Table 2. In alkaline or neutral solution lactic acid and the volatile fatty acids are very ineffective. If it were not for evaporation, therefore, sweat would rapidly lose the mild antiseptic action it might originally have had. On incubation of sweat, ammonia nitrogen may rise from 5 mg. or less per 100 cc. to 25 mg. or more. This amount of ammonia is sufficient to account for the neutralization of lactic and other acids that occurs in the incubation.

On evaporation of incubated sweat the pH gradually falls. Thus a specimen of sweat with a pH of 6.1 on incubation for 18 hours had a pH of 7.0, and on concentration at 40° C. in a current of air came back to 5.9. Other cases where concentration and incubation went on together over a period of about 6 to 8 hours gave final pH values of near 5.0. Such tests may more nearly approximate conditions occurring on the skin.

The change from alkaline to acid solution on evaporation is apparently due to the fact that lactic acid is non-volatile and the so-called volatile fatty acids are also less volatile than ammonia, so that ammonia passes off leaving most of the acids behind. Thus a specimen of sweat having an ammonia concentration of 6 mg. per 100 cc. was incubated at 40° C. for 18 hours and ammonia went up to 24 mg. per 100 cc. The

incubated sweat was concentrated 50 times by evaporation at 40° C. and ammonia fell to 8 mg. The instability of the ammonium salts of the acids involved is well recognized.

That the pH of sweat is not due to any great extent to the presence of carbon dioxide is indicated by the fact that when air free from carbon dioxide was bubbled for 15 minutes through samples of sweat kept at 60° C. there was a change of only about 0.1 in the pH of the sweat (as from 6.1 to 6.2).

The Volatile Fatty Acids. Determination of the total volatile fatty acid of sweat is a relatively simple procedure. Characterizing the individual fatty acids present is difficult, especially with the small amounts present in sweat. Peck *et al.*[3] give figures for per cent of various acids as acetic 0.0096, propionic acid 0.0062, caprylic and/or caproic acid 0.0046. Since methods of analysis are not given it is not clear whether formic and butyric acids were found absent or are included in the above fractions. Using the method of Werkman[4] we obtain figures corresponding to 75 to 90% acetic acid and 10 to 25% of propionic or butyric acids. More work on this point is needed but since acetic acid appears ordinarily to definitely predominate, and the antibacterial actions of butyric and propionic acids appear not to be greatly different, no large error of interpretation is likely to be involved in this uncertainty, nor even by the assumption that the total volatile acids will be just slightly more effective than an equivalent amount of acetic acid.

To determine whether the volatile acids were original constituents of the sweat secretion or were formed on the surface of the skin two types of experiments were made. In one series the heat sweat was collected in 2 or 3 successive portions of 100 cc. or more each. The first sweat together with the previous scouring should have washed off most of the adherent perspiration so that later samples should be a purer secretion. The pH values and total volatile acids of first and final sweat samples in 5 cases are given in Table 1.

TABLE 1.—THE PH VALUES AND TOTAL VOLATILE ACIDS OF FIRST AND FINAL SWEAT SAMPLES

	First sweat specimen		Final sweat specimen	
Subject	pH	Volatile acids (normality)	pH	Volatile acids (normality)
1	5.45	0.004	6.15	0.002
2	5.38	0.009	6.10	0.004
3	5.60	0.002	6.00	0.002
4	5.30	0.001	6.10	0.001
5	5.10	0.001	5.60	0.0007

It will be noted that volatile fatty acids decreased on repeated sweating except where the value was already low. In many other cases also, where but one specimen of sweat was obtained the total volatile acids were in the neighborhood of 0.001 N, a very low value. The lowest value obtained was 0.0007 N. It is not excluded that still lower values might be obtained by still better preliminary cleansing of the skin and decreasing to a minimum the degree of bacterial action permitted during collection of the specimen. It is therefore doubtful

whether any appreciable amounts of volatile acids are actually secreted in sweat. This is in line with the finding of practically no volatile acids in urine, where lactic acid is however found. Apparently the volatile acids formed in metabolism are very rapidly oxidized in the body so that they do not accumulate in the blood or appear in the urine.

If the volatile fatty acids are not excreted in sweat or only in small amounts they must be formed on the skin by bacterial action. Experiments on the incubation of sweat support this view. Sweat was incubated at 37° C. for 18 hours. Some results follow:

TABLE 2.—CHANGES IN SWEAT ON INCUBATION

Subject	pH		Volatile acids (normality)	
	Before	After	Before	After
1	6.95	8.00	0.0037	0.0100
2	6.46	7.00	0.0010	0.0035
3	5.75	7.17	0.0022	0.0084
4	6.15	7.46	0.0020	0.0060
5	5.38	8.05	0.0090	0.0125
6	6.10	8.30	0.0043	0.0105
7	6.10	7.00	0.0010	0.0025
8	5.30	5.90	0.0010	0.0028

It is evident that the volatile fatty acids of sweat may increase markedly on incubation and it appears that most if not all of the volatile acids found in sweat that has remained for some time on the surface of the body must be due to bacterial action.

That the volatile fatty acids are largely formed by bacterial action on the lactic acid of the sweat is indicated by the fact that on incubation of sweat the fatty acids rise and the lactic acid decreases to about the same extent (Table 3). A similar formation of fatty acids from lactic acid occurs in the intestines. While it is not certain that all of the fatty acids are formed from lactic acid, it is not clear from our knowledge of the chemistry of sweat just what other constituent might yield fatty acid. No study has been made of the bacteria concerned. Incubation of sweat made sterile by Berkefeld filtration causes no decrease in lactic acid or increase in volatile acids.

TABLE 3.—EFFECT OF INCUBATION OF SWEAT ON LACTIC ACID AND ON VOLATILE FATTY ACIDS

(Incubation for 24 hours at 37° C. Results expressed in normality)

No.	Sweet lactic acid		Volatile fatty acid		Lactic acid decrease	Volatile acid increase
	Before incubation	After incubation	Before incubation	After incubation		
1	0.018	0.015	0.001	0.003	0.003	0.002
2	0.025	0.018	0.002	0.006	0.007	0.004
3	0.028	0.022	0.002	0.005	0.006	0.005
4	0.018	0.017	0.001	0.002	0.001	0.001

The volatile acids do not therefore appear to be primary constituents of sweat and amounts present are naturally variable. That nevertheless the volatile acids may be significantly antibacterial upon the skin has been indicated by the work of Peck *et al.* Our work on the fatty acids indicates in some detail what conditions must exist with regard to them if they are to be effective. It is doubtful whether they ever

have much influence simply through their effect upon the pH of the sweat since they are commonly present in definitely smaller amounts than lactic acid and are weaker acids. Their influence must be due chiefly to undissociated molecules of the acids and will depend upon the nature of the acid and upon its dissociation which in turn depends upon the dissociation constant of the acid and upon the pH. Thus acetic acid has an ionization constant of 1.85×10^{-5}. If we start with 0.1 N acetic acid (pH 2.89) and add NaOH to obtain a hydrogen-ion concentration of 1.85×10^{-5}, (pH about 4.7) there will be an equal number (0.05 N) of acetic acid molecules and of acetate ions. Neutralizing to pH 5.7 the acetic acid molecules would be about $\frac{1}{5}$th as great (0.09 N) and at pH 6.7 about $\frac{1}{50}$th as great. Acetic acid is thus very effective at pH 5, fairly effective at pH 6, but becomes rapidly ineffective above that point. Lactic acid having an ionization constant of 1.4×10^{-4} would be half in the molecular form and hence have a high molecular effect at pH 3.85. It would have a fair effect at pH 4.85, but a low effectiveness at pH 5.85 or higher. There is thus a range of about pH 5.4 to 6.2 where lactic acid tends to be ineffective but acetic acid (also propionic and butyric acids) may still exert an appreciable influence on bacterial growth.

Where the lactic acid of the sweat succeeds in maintaining a pH of 5 or lower its effect may predominate, but when it falls to around pH 6 from any cause the volatile acids may be more important. The volatile acids thus form a sort of "second line of defense." This is essentially the same thing that occurs in the intestines where lactic acid production from carbohydrate may inhibit some bacterial growth, but as this acid is absorbed or neutralized to a pH in the neighborhood of 6, the production of volatile acids from the lactic acid extends the protection to these higher pH levels. As in the intestines the situation is quite complicated, making difficult an exact evaluation of the importance of the volatile acids in a given case. We have variations in amount of sweat secreted, in the composition of this sweat on different areas of the skin, in the degree and rapidity of evaporation, and in the character of the skin flora. Pathologically also the resistance of the organisms concerned in the skin pathology must be involved as well as any influence of pathology on perspiration. We have published results on the resistance of a variety of organisms to the volatile acids.[1a,b] Peck *et al.* have published results with certain fungi.

Of the 18 organisms studied by us, many were inhibited by 0.005 N volatile fatty acid at pH 5.4 to 5 or lower and most of them by 0.01 N volatile fatty acid at pH 5 or lower. Seven organisms were inhibited by 0.025 N butyrate at pH 6.4, and 11 at pH 6.0. A sweat containing 0.025 N volatile fatty acid and hence effective against many organisms in the neighborhood of pH 6 could readily be formed by evaporation of fresh or incubated sweats to from $\frac{1}{5}$th to $\frac{1}{10}$th their volumes and where such conditions are found upon the skin a protective action may be postulated. At reactions above pH 6.5 such protection must be very slight no matter what amount of lactic or volatile acids may be present.

Peck *et al.* have reported some success in the use of volatile acids in the therapy of certain skin disorders. We believe our reports have added something to the rationale of such use by emphasizing the limits of pH at which effectiveness of the various acids may be expected and by pointing out that buffer solutions of these acids should be much preferable to use than the pure acids because their buffering effect helps to maintain the given acidity and because the irritant effect of low pH in itself is much decreased. Thus solutions of the volatile fatty acids, especially acetic and propionic from 0.01 to 1 N neutralized to from pH 4.5 to 6.0 should be given further trial. As antiseptics such solutions have the advantage of low toxicity.

Studies on the pH, lactic and other acid concentrations on various skin areas, with special reference to certain types of skin disorders, are being carried out as well as studies of the conditions under which applications of buffer solutions of the acids may be useful.

Summary. An effort has been made by the application of previous findings from this laboratory on the factors governing the antibacterial action of the volatile fatty acids to clarify the relation of these substances to the antiseptic action of sweat. While interpretation is complicated by the variety of factors involved, the general picture seems to be as follows: Freshly secreted sweat may have a mild antiseptic action due largely to its acid pH, for which lactic acid is largely responsible. Evaporation of such sweat on the surface of the skin or elsewhere tends to lower the pH and increase the lactic acid concentration, so that the sweat becomes much more effective in this regard. Tests on incubation of sweat show, however, that there is also a tendency for the sweat to become alkalinized, due to ammonia formation by bacteria from the urea present. Ammonia is more volatile than lactic acid, however, so that on evaporation much of this ammonia is lost and the lactic acidity regained. The volatile fatty acids are largely if not entirely formed on the surface of the skin by bacterial action upon the lactic acid. Above pH 5.3, lactic acid is so completely ionized that few undissociated molecules of acid (on which much of the antibacterial action of the acid must depend) are present. The chief protective value of this acid lies therefore below pH 5.3. The volatile acids are less dissociated (and hence more effective) in the pH range of 5.3 to 6.2 Their most important rôle would appear therefore to be the extension of some degree of acid protection into these higher pH levels which also exist on the skin under certain conditions.

Conclusions. Sweat as secreted contains lactic acid in amounts sufficient to give it some bactericidal action. Evaporation on the skin increases the lactic acid concentration and renders the sweat much more effective. The concentration must be such as to give a pH of 5.3 or lower for the lactic acid to have much effect. The volatile fatty acids of sweat appear to be formed by bacterial action on the lactic acid. They are present in smaller amounts than lactic acid in sweat but are relatively more effective in the range of pH 5.3 to 6.2. They may therefore extend the antiseptic action of the sweat into the regions of the skin where this pH range prevails and thus act as an additional

safeguard against skin infections. This can be of some importance in such regions as the axillæ which are relatively less acid. Chemical changes occurring in sweat after secretion are discussed.

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THE PRESENT POSITION OF GASTROSCOPY IN THE DIAGNOSIS OF GASTRIC DISEASE*

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My teaching and consultation experiences indicate that many clinicians are still unaware of the position of gastroscopy in the diagnosis of gastric disease despite an increasing literature on the subject. This may be due in part to the recentness of the revival of gastroscopy and in part to the fact that many of the publications are written for specialists in the field. This article is written to point out simply and clearly when gastroscopy might be employed and when not, and what might be expected from it.

Gastroscopy is the direct visualization of the surface of the stomach by means of an illuminated instrument. It is almost the oldest of endoscopic methods, but the most recent to tend toward perfection through the development in 1932 by Georg Wolf and Rudolf Schindler[8] of a flexible gastroscope. Gastroscopy began in 1868 when Kussmaul first attempted it by means of a straight tube; Mikulicz in 1881, Rosenheim in 1895, and Elsner in 1911 were pioneers. All attempts were unsatisfactory due to technical difficulties: these consisted chiefly in the inability to construct a satisfactory optical system; in accidents, particularly to the esophagus; and in diagnostic limitations, in that only a small portion of the large surface of the stomach was visible.

The flexible gastroscope came into being when it was learned that one could see through a curved tube if lenses of a very short focal distance were used. The instrument is 77 cm. long and 11 mm. in diameter, no larger in diameter than the large Ewald tube. Its advantage lies in the fact that when it is fully inserted there is an angle of deviation of 90° and an angle of vision of 85° so that one can see almost at right angles. The danger of perforation of the esophagus has been almost obviated because when fully inserted, the flexible

* Thanks are due Dr. Rudolf Schindler, of Chicago and Dr. Harold E. Wright, of Baltimore for their critical analyses of this paper.

portion is at least 3 cm. above the cardia where damage is most likely to occur. An instrument with an angle of vision of 45° is also made. Here the magnification is greater.

The survival rate of new clinical procedures is low. Survival depends on 4 considerations: (1) safety, (2) ease of accomplishment, (3) freedom from gross discomfort, and (4) production of results of value. As will be seen, gastroscopy has met all of these requirements.

1. *Safety.* Sixty gastroscopists performing 22,351 examinations in the United States, England and Australia reported to Schindler[9] who inquired as to the safety of the procedure that there had been only one death. This followed perforation of the hypopharynx in a patient who had been bronchoscoped a week previously; this represents a mortality rate of 0.004%. There were also 8 perforations of the stomach and 1 perforation of the jejunum in a resected stomach, all with recovery. To this may be added 2 gastric perforations with recovery, 1 in 100 gastroscopies by Segal[11] and the other in more than 500 examinations by Schiff.[7] These figures speak decisively for the relative safety of gastroscopy.

2. *Ease of Accomplishment.* The routine varies and in many places it is still unnecessarily elaborate. In my own hands simplicity has been the keynote. If there is no gastric residue, the patient may take food until 8 o'clock of the night preceding the morning of examination. When there is gastric residue, adequate aspiration and if necessary lavage must take place the night before. The only conditions in which gastroscopy should not be attempted are those involving the inability to pass the largest Ewald tube (11 mm.) easily into the stomach, aneurysms of the aorta and lesions of the esophagus: stricture, cardiospasm, cancer, varices. These, save for varices, can be determined by fluoroscopy alone and esophageal varices are almost never present except in the face of obvious hepatic disease. Therefore preliminary esophagoscopy is unnecessary. When dyspnea, cardiac decompensation, asthma, angina pectoris, esophageal diverticuli, kyphosis or scoliosis are present, the examiner must weigh their contraindications against the need of gastroscopy.

About 45 minutes prior to instrumentation the patient is given $\frac{1}{4}$ gr. of morphine and $\frac{1}{75}$ gr. of atropine. One-half hour after morphine and atropine, his tongue, buccal mucosa, gums, lips and pharynx are painted with 2% pontocaine hydrochloride by means of a curved camel-hair brush. Aspiration of the stomach contents is then performed, the large Ewald tube being used. The patient is then placed on an ordinary table on his left side with his left arm flexed under the left lateral aspect of the thorax. The knees are also flexed. Finally the instrument is inserted. Some examiners have a nurse or a technician hold the patient's head; this is not essential. As in cystoscopy, so in gastroscopy, the organ to be examined must be distended. In cystoscopy, the medium employed is water; in gastroscopy, the walls are separated by inflation with air. In short, the preliminary proceedings and actual technique are simple. The problem is not in the insertion of the gastroscope; it is in orientation and in interpretation which

require training and experience. Schindler's excellent monograph will be helpful in this connection.[8]

3. *Freedom From Gross Discomfort.* The examination is a matter of a few minutes. The use of the operating room is totally unnecessary. The ambulatory patient leaves a few minutes after the procedure without difficulty. He may have a sore throat which may appear after the anesthetic influence of pontocaine hydrochloride is no longer present, and it may persist for 12 to 24 hours. He is permitted to eat when anesthesia is no longer present, about 2 hours after its application, so that food, by virtue of the absence of the essential reflexes, will not pass into the trachea or bronchial tree.

4. *Production of Results of Value.* The question now arises as to what is to be gained by gastroscopy. Since it in no way rivals the Roentgen ray examination, is not expected to take its place, and is a complementary procedure, what does it add? This phase will now be discussed in association with the limitations of the procedure and the data procured by roentgenology.

Gastroscopy, like all other procedures, has definite limitations. Jankelson and McClure,[2] both excellent gastroscopists, have reminded us of these: gastroscopy visualizes only the mucosa; biopsy specimens cannot be obtained through the gastroscope nor has photography through it been perfected; small localized lesions may not be steadily seen due to changes in peristalsis and respiratory movements; lesions occurring with relative frequency and often malignant at the lesser curvature of the antrum are not always detectable by the gastroscope; there is difficulty at times in visualizing a niche on the lesser curvature of the upper third of the stomach; on occasion it may be impossible to distinguish between a benign or a malignant ulceration and between hyperplastic gastritis and cancer. Sometimes a stoma cannot be seen and a marginal ulcer on the jejunal side is missed. The distal portion of an hour-glass stomach cannot be inspected. There are a small group of patients temperamentally unfit for this procedure. These limitations in actual practice are not as formidable as they would seem. Since there is no perfect procedure, limitations are always to be weighed in relation to the accruable benefits. In the final analysis it is not what cannot be seen but what can be seen with this instrument that makes it so important. Experience and repeated examinations reduce some of these limitations. Those temperamentally unsuited for the procedure usually respond poorly to any other endoscopic or even more simple procedures. The use of pentothal sodium intravenous anesthesia may solve this problem.

Roentgen Ray Examination. Except in unusual circumstances, this should always precede gastroscopy. When is the latter to be instituted and what is to be expected of it in the presence of negative, positive, or inconclusive Roentgen ray findings?

1. *Negative Roentgen Ray Findings.* Gastroscopy is in order whenever the Roentgen ray findings are negative and there is a persisting suspicion of some abnormality. Whenever malignancy is a possibility because of such symptoms as discomfort with loss of weight or vitality,

anorexia, anemia and fever, this procedure is obviously indicated. A small number of malignancies and peptic ulcers may thus be detected. For instance, Lintott[3] of Guy's Hospital in London reports that of 92 chronic gastric ulcers, 8 were encountered by gastroscopy which were negative by Roentgen ray, 2 were missed by gastroscopy which were seen by Roentgen ray and in all others there was agreement.

Roentgen ray is sometimes negative in the presence of hemorrhage. Undetermined hematemesis or melena may sometimes be explained by gastritis. Roentgen ray is not dependable in the diagnosis of gastritis, gastric analysis will not establish it and the gastroscope is the only reliable means of detection. In Germany it is stated that gastritis is responsible for 10% of all massive hemorrhages. There is some debate as to how soon gastroscopy is to be instituted following unexplained hematemesis or melena. My own practice is to do it just as soon as the initial shock is over. If one waits too long, acute lesions may be healed. Therefore, it is sometimes advisable to perform gastroscopy prior to roentgenology which is usually done a week or longer after hemorrhage.

Ill-defined complaints and a symptom-complex like that of duodenal ulcer will often be diagnosed as functional in character if the physical examination, roentgenology and other studies throw no light on structural change to account for them. Several types of gastritides have been found among this group since the advent of the flexible gastroscope. At this writing, it is not generally agreed as to the extent to which gastritis may account for complaints. Nevertheless it is important to know whether this condition is present or not. Some believe that atrophic and superficial gastritis frequently do not produce the digestive symptoms complained of, and here the patient as a whole must be treated rather than the gastritis. Even hypertrophic gastritis in some patients may never cause symptoms. These objective findings must be interpreted cautiously and in relation to the entire clinical picture.[5,6]

Gastroscopy is further indicated in a small group of individuals who despite the usual assurances of the absence of structural change are unwilling to accept this in the presence of persisting symptoms. Negative gastroscopic findings enabling additional reassurances often puts them at ease.

2. *Positive Roentgen Ray Findings.* Even here, under certain circumstances, gastroscopy has its place. Not infrequently gross differentiation of benign lesions from malignant growths is made more correctly through the gastroscope than by Roentgen ray or at operation or from the gross resected tissue seen in the laboratory. For instance, Clerf and Wirtz[1] of the Jefferson Hospital in Philadelphia in a series of 34 patients with gastric cancer and gastric ulcer selected because the gastroscopic examination was essential in making a diagnosis, found that the Roentgen ray diagnosis in one patient was benign ulcer, in another malignancy was suspected and in the third no lesion was demonstrated by Roentgen ray; in each a diagnosis of carcinoma was made gastroscopically and verified histologically. The reason is

that through the gastroscope actual living tissue with undisturbed blood supply is seen. The appearance is different when the circulation is destroyed.[10] I have heard urologists say that this situation is also true in cystoscopy, that the lesion and its gross differentiation is often better seen through the cystoscope than with the specimen in one's hand. These observations are not to be taken to mean that the final decision as between benign and malignant lesions is to be determined by its gastroscopic appearance. The appearances upon repeated examinations and the response to therapy may be the guiding factors. Obviously, the microscopic examination of the tissue offers the final word.

By Roentgen rays it is frequently difficult to differentiate spasm and edema associated with the lesion from the lesion itself; with the gastroscope the distinction may often be made more nicely. By gastroscopy one may be able to determine more clearly the question of operability; the decision may depend not only upon the site but also upon the extent of the involvement.

Even where duodenal ulcer is established by Roentgen ray but the clinical picture is atypical, gastroscopy is indicated because of the possibility of an associated gastritis. This manifestation is absent in a majority of such cases, but its presence should be known.

3. *Inconclusive, Incomplete and Inconsistent Roentgen Ray Findings.* Roentgen ray findings may not be conclusive in themselves or may be inconsistent in relation to the clinical picture. Gastroscopy is definitely indicated under these circumstances. For instance, when the Roentgen rays indicate an obstruction at the outlet of the stomach, it may be difficult to determine whether there is a lesion in the pyloric sphincter, in the duodenum, or in the gastric side of the sphincter. The location of the lesion is extremely important: if it can be localized to the first portion of the duodenum, it is almost certain to be benign; if it is in the pyloric ring, it may or may not be benign; if it is in the antrum, it is likely to be malignant. A normal pyloric ring, by gastroscopy, would be strong evidence in favor of a normal pyloric sphincter and with a normal antrum, the lesion could more readily be localized to the duodenum. At times, the typical clinical picture of uncomplicated duodenal ulcer may become modified; this may be due to gastritis demonstrable usually only by the gastroscope and the deformed duodenal bulb may be an indication of a previous ulcer. Frequently deformity without a persistent niche or crater is reported by Roentgen ray along the lesser curvature of the stomach. Is it active or it is scar tissue and are the symptoms on this or on another basis? The question can frequently be answered if visualization by gastroscopy can be made.

Those patients manifesting bizarre or atypical Roentgen ray filling defects and defects suspected of being extragastric should be gastroscoped with a view toward further clarification. Foreign bodies or polyps may sometimes best be detected by gastroscope.

Treatment of Benign Gastric Ulcer. The gastroscope has its place even here, for it is well known that the Roentgen ray indication of healing does not parallel the evidence obtained by the gastroscope.

The niche or crater may disappear in the roentgenogram within 2 to 4 weeks on medical management. The explanation is that inflammation and spasm account for much of the Roentgen ray defect which is often quickly corrected. However, epithelialization as noted by gastroscopy takes 6 to 8 weeks and sometimes longer. Hence no lesion demonstrable by the gastroscope should be considered healed unless this is evident by the gastroscope. This requires repeated gastroscopic examinations during the course of treatment.

Gastroscopy is Indicated Preoperatively and Postoperatively. 1. *Preoperatively.* It is necessary to ascertain whether in association with benign ulcer there is widespread gastritis, any additional ulceration or erosion not seen by Roentgen ray. While surgical intervention may relieve a not too extensive gastritis, it may also result in its exaggeration through altered anatomic and physiologic relationships. Hence such information is important for adequate evaluation of the problem. The differential diagnosis between benign and malignant lesions and the presence or absence of a lesion upon which an operation is planned has already been referred to.

2. *Postoperatively.* Any patient complaining of distress following gastric operations should be studied with the gastroscope following Roentgen ray examination. Roentgen ray under these conditions may sometimes be difficult of interpretation because of variations in the contour of the stomach incident to the operation and repair. Moersch and Walters[4] found by gastroscopy, gastritis in 56 of 100 cases suffering from dyspepsia following various types of gastric surgery. No doubt a preoperative gastritis existed in some. In a majority with gastroenterostomy, the stoma can be viewed by gastroscopy; ulceration, gastritis and jejunitis if present can usually be demonstrated. Following subtotal gastrectomy for cancer or ulcer, recurrence of symptoms is an indication for gastroscopy in order to determine the presence of ulcer or gastritis or recurrence of malignancy, the earliest evidence of which may be detected by gastroscopy.

In general, gastroscopy is further indicated in all adults particularly over 40 complaining of ill-defined or mild digestive symptoms involving anorexia, loss of weight, nausea, vomiting, low grade fever and anemia. An early diagnosis of gastric malignancy may be made by this method.

Summary. Gastroscopy has become a permanent addition to our diagnostic armamentarium because of its safety, simplicity, the relative absence of gross discomfort and the production of results of value.

1. Gastroscopy is complementary to Roentgen ray in diagnosis. *A.* When the Roentgen rays are negative and yet suspicion of abnormality persists, gastroscopy may reveal an occasional malignancy, erosions, peptic ulceration or gastritis. These lesions may also account for otherwise unexplained hemorrhage and a duodenal ulcer symptom-complex not due to duodenal ulcer.

B. When Roentgen rays are positive, gastroscopy makes possible: (1) confirmation; (2) a nicer gross differentation between benign and malignant lesions; (3) a clearer delineation of the site and extent of the lesion which helps to determine the question of operability; (4) the

differentiation grossly of spasm and edema from the lesion itself; (5) the occasional detection of an associated gastritis which may account for atypical symptoms often erroneously ascribed to a Roentgen ray defect in the duodenal cap actually due to a healed, scarred ulceration.

C. When Roentgen rays are inconclusive, incomplete, inconstant, bizarre or atypical, gastroscopy may make possible: (1) a more accurate diagnosis of the presence or absence of a lesion; (2) the nature of a lesion responsible for an obstruction at the outlet of the stomach; (3) the presence of gastritis possibly accounting for a modification in the clinical picture of what would seem by Roentgen ray to be an uncomplicated duodenal ulcer.

D. In hemorrhage, gastroscopy may be instituted before acute lesions heal and prior to Roentgen rays.

2. Gastroscopy is often indicated preoperatively, even in the presence of positive Roentgen rays because it is desirable to know whether there is an associated gastritis or any additional ulcerations, erosions or masses not shown by the Roentgen rays.

3. Postoperatively: In gastro-enterostomy or in subtotal gastrectomy the return of any digestive complaints is an indication for gastroscopy. Ulceration, gastritis and jejunitis are usually readily detectable and the recurrence of a malignant lesion in the stomach may be first detected by gastroscopy. Here gastroscopy is particularly important because changes in the contour of the stomach incident to operation make roentgenologic interpretations difficult.

4. Gastroscopy is essential in determining the progression and healing of gastric ulceration.

5. Unexplained anorexia, loss of weight, nausea and vomiting, low grade fever and anemia are indications for gastroscopy. The earlier diagnosis of cancer may thus be made possible.

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MALIGNANT TUMORS IN PERSONS WITH CIRRHOSIS OF THE LIVER

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Rats fed on a diet containing carcinogenic azo-compounds, especially butter yellow, develop cirrhosis of the liver and hepatomas,[2,8] unless the diet is enriched with a certain amount of bread, fresh liver, yeast,

or riboflavin and casein.[3,4,9] These results revived the question whether and how dietary measures can be utilized in prevention of human cancer.[5] A statistical analysis of the relationship between malignant tumors and cirrhosis in man seems, therefore, pertinent.

The postmortem records of the Bellevue Hospital, New York City, were studied for the period from March 1934 to February 1941. All cases over 20 years of age excluding those only partially examined were surveyed. There were 6596 cases; of them 4808 males and 1788 females.

Cirrhosis of the Liver. Cirrhosis was found 608 times (9.2%) in this series of autopsies. Of the cirrhotics, 37 men and 24 women had died in the age group 20–39 years, 221 and 84, respectively, in the age of 40–59 years, and 184 men and 57 women had died in the age group of 60 and more years. According to Table 1, the youngest age group, of the men examined postmortem 5%, and of the women 5.4% had cirrhosis; the corresponding figures in the middle age group were 9.8% and 11.6%, and in the highest age group 10.3% and 9.2%, respectively.

These figures refer to cirrhosis, regardless of whether or not this was the cause of death. In statistics of causes of death, cirrhosis appears in but $\frac{1}{7}$ or $\frac{1}{8}$ of our percentage.[1]

For several reasons neither of both sources correctly pictures the frequency of cirrhosis in the population. In this series, 178 cases—29.5% of male, and 28.5% of female cirrhotics—were classified as early cirrhosis. Such cases remain undetected without autopsy, and may be in the general population more frequent than in our series. Furthermore, of the fully developed cases of cirrhosis a considerable portion die of other diseases, and thus enter the statistics of causes of death under various headings. In studying the relationship between cirrhosis and malignant tumors this has to be taken into account. On the other hand, even in a general hospital the necropsy material is a selection of cases, and thus cirrhosis may appear more frequently than is truly representative, and the proportions to other diseases may become distorted. One has to bear this in mind in order to omit improper conclusions.

In 473 cases a diagnosis of Laennec cirrhosis was made, 45 cases were designated as biliary cirrhosis, 10 as syphilitic, and 5 as fatty cirrhosis; in 75 cases no detailed classification was given.

Malignant Tumors of the Biliary System and of the Pancreas. As anticipated, malignant tumors of the liver appear in the cirrhotics much more frequently than in the remainder of the entire series of 6596 cases. Likewise, malignant tumors of the extrahepatic bile passages and of the pancreas occurred more frequently among cirrhotics.

Of 4365 males without cirrhosis, 17 ($0.39 \pm 0.08\%$) had a primary intrahepatic tumor,* while among 443 males with cirrhosis 18 ($4.06 \pm 0.93\%$) such cases were found. Male cirrhotics exceed the non-cirrhotics by 3.67 hepatic tumors per 100, with a critical ratio

* Of these tumors one was an angiosarcoma (in a 47-year-old negro), the remainder were carcinomas.

of 4, which is highly significant.* Adjusting the age distribution of cirrhotics to that of non-cirrhotics, one finds the crude rate of 4.06% to change to 3.94±0.93%†. In women, the difference in intrahepatic malignant tumors is smaller; the corresponding values for 1623 non-cirrhotics being 5=0.31±0.13%, and for 165 cirrhotics 2=1.21% (crude), and 1.08±0.81% (age adjusted), respectively.

Out of the 20 cases of cirrhosis associated with intrahepatic carcinoma, 15 were classified as Laennec type, 3 as biliary, and 2 as cirrhosis without further specification. Of the 20 cases, only 1 (a female) was designated as early cirrhosis.

TABLE 1.—MALIGNANT TUMORS OF THE LIVER AND OF INTRAHEPATIC BILE DUCTS

	Age at death, yrs.			
	20–39	40–59	60–	Total
Men without cirrhosis of liver:				
All cases	702	2032	1631*	4365
Tumor cases: No.	2	7	8	17
%	.28	.34	.49	.39
Men with cirrhosis of liver:				
All cases	37	221	185†	443
Tumor cases: No.	1	9	8	18
%	2.7	4.1	4.3	4.1
Women without cirrhosis of liver:				
All cases	419	642	562‡	1623
Tumor cases: No.	..	3	2	5
%	..	.47	.36	.31
Women with cirrhosis of liver:				
All cases	24	84	57	165
Tumor cases: No.	..	1	1	2
%	..	1.2	1.75	1.2

* Among them 29 cases of unknown age.
† Among them 4 cases of unknown age.
‡ Among them 1 case of unknown age.

In the non-cirrhotic group, malignant tumors of the extrahepatic bile passages and pancreas were encountered 63 times, *e. g.*, in 0.89±0.10% of males, and in 1.48±0.30% of females; in the cirrhotic group—with 18 such cases—the corresponding age adjusted values are 2.66±0.77% and 2.76±1.28%, respectively. In males the difference is considerable and 2.3 times the critical ratio, *e. g.*, statistically significant; in females the difference is smaller and insignificant.

Of the 18 cases of cirrhosis of the liver associated with a primary malignant tumor in the extrahepatic biliary organs or pancreas, 4 were classified as of the Laennec type (of them one early), and 14 as biliary cirrhosis (of them 6 early). In this group of tumors the portion of early cirrhosis is much higher than in persons with an intrahepatic malignant tumor.

Malignant Tumors of All Other Organs. Although there is a discrepancy between clinical observations and experimental results, cirrhosis has been persistently linked with chronic alcoholism.

* Critical ratio is the difference between two values divided by their standard error of the difference. A ratio of 2 and more is significant. A critical ratio of 4 indicates a probability of chance result as 1 in 16,000.

† Crude, *e. g.*, the actual percentage; age-adjusted percentage, *e. g.*, the figure as it would be in a group of cirrhotics of the age distribution of the non-cirrhotics.

In male alcoholics, malignant tumors of the mouth, pharynx, larynx, and esophagus are more frequent than in the general population.[6,7] It is, therefore, of interest that of 443 male cirrhotics in this series 12 (*i. e.*, 2.71±0.70%) had a malignant tumor in one of these sites while the corresponding percentage in 4365 non-cirrhotics was 1.99±0.22% (86 cases). The difference is statistically insignificant, indicating that for this purpose the material is too small to yield definite results. Of the 12 cases 2 had early cirrhosis.

TABLE 2.—MALIGNANT TUMORS OF EXTRAHEPATIC BILE PASSAGES AND OF PANCREAS

	Age at death, yrs.			
	20-39	40-59	60-	Total
Men without cirrhosis of liver:				
Tumor cases: No.	1	17	21	39
%*	.14	.83	1.28	.89
Men with cirrhosis of liver:				
Tumor cases: No.	..	4	9	13
%*	..	1.81	4.86	2.93
Women without cirrhosis of liver:				
Tumor cases: No.	1	5	18	24
%*	.24	.78	3.21	1.48
Women with cirrhosis of liver:				
Tumor cases: No.	..	2	3	5
%*	..	2.38	5.26	3.03

* In per cent of all cases examined postmortem (see Table 1).

In males examined postmortem, no other group of organs shows an increased frequency of malignant tumors. Neoplasms of intestines are equally represented in both male groups, while in all other organs including stomach malignant tumors are found in 11.25±0.47% of men free of cirrhosis, and in only 5.19±1.06% of cirrhotics.

In females, tumors of the mouth, pharynx, larynx and esophagus are too rare for a statistical analysis. In this series there were altogether 10 such cases. As to the malignant tumors of other organs (see Table 3, Cols. 3–5), their percentages are smaller in those afflicted with cirrhosis, the difference being negligible as far as intestines and genital organs are concerned, a little larger with regard to the breast, and considerably larger in other organs. This difference is in women as well as in men highly significant, being 3.3 and 5.4 times the critical ratio, respectively.

TABLE 3.—MALIGNANT TUMORS IN VARIOUS GROUPS OF ORGANS (PER 100)

	Biliary system and pancreas Col. 1	Mouth pharynx, larynx and esophagus Col. 2	Intestines* Col. 3	Inner female genital organs Col. 4	All other organs† Col. 4	All organs Col. 5
Men without cirrhosis of liver:						
Of whole series	1.3	2.0	2.45	..	11.25	17.0
Men with cirrhosis of liver:						
Of whole series	7.0	2.7	2.5	..	5.2	17.4
Women without cirrhosis of liver:						
Of whole series	1.8	0.6	3.3	2.6	9.2	17.4
Women with cirrhosis of liver:						
Of whole series	4.2	..	3.0	2.4	4.2	13.9
Men with malignant tumor:						
Without cirrhosis of liver	7.5	11.7	14.4	..	66.4	100.0
With cirrhosis of liver	40.3	15.6	14.3	..	29.8	100.0

* From the duodenum to the anus.
† Including hematopoietic system.

TABLE 4.—MALIGNANT TUMORS IN ORGANS OTHER THAN BILIARY AND PANCREAS

	Age at death, yrs.			
	20–39	40–59	60–‡	Total
Men* without cirrhosis of liver:				
No.	46	287	353	686
%†	6.6	14.1	21.6	15.7
Men* with cirrhosis of liver:				
No.	1	15	30	46
%†	2.7	6.8	16.2	10.4
Women* without cirrhosis of liver:				
No.	44	112	98	254
%†	10.5	18.0	17.5	15.6
Women* with cirrhosis of liver:				
No.		5	11	16
%†		6.0	19.3	9.7

* The total number of examined postmortem is given in Table 1.
† In per cent of all cases examined postmortem.
‡ Those of unknown age (see Table 1).

In the postmortem material the percentage distribution of malignant tumors does not correspond with that in the general population. Because of less interest in carcinoma of the stomach, in necropsies this type of tumor is less frequent, while lung tumors for instance are more often recorded. However, a carcinoma of the stomach combined with cirrhosis is not less interesting than one without cirrhosis. The same can be said with regard to leukemia, which are included in the malignant tumors. There were 36 males and 14 females who had leukemia among non-cirrhotics, but no case among cirrhotics.

Altogether, in persons free of cirrhosis, malignant tumors in organs other than biliary tract and pancreas are found with equal frequency in males and females (15.66%*). The crude as well as the age adjusted values for cirrhotics are much lower; 10.4 and $9.6 \pm 1.3\%$, respectively, for men, and for women 9.7 and $8.6 \pm 2.0\%$, respectively. Not all 3 age groups present the same relationship. As seen from Table 4, the difference in the frequency of malignant tumors changes inversely with age. For instance, in the 20–39-year old males, the difference between cirrhotics and non-cirrhotics is $6.6–2.7=3.9$, which is almost two-thirds of the value of 6.6%, while in the highest age group the corresponding figures are $21.6–16.2=5.4$, which is only one-quarter of the value of 21.6%.

Ratio of All Malignant Tumors. In the entire series there were 1125 cases of malignant neoplasm (17%); men having approximately the same ratio as women. As seen from Tables 3 and 5, in male cirrhotics the percentage of all malignant tumors is the same as in male non-cirrhotics, while in women there is a statistically insignificant difference in favor of the cirrhotic group. In the two younger age groups, malignant tumors are more frequently encountered in persons without cirrhosis; in the highest age group the relation is reversed.

The Race Factor. Of the 6596 cases of this series, 867† were colored, mostly negroes, Chinese and Japanese. On the average, at the time

* Without leukemia there were 14.84%.
† 559 men and 314 women.

of death, members of the colored races were 9 and 12 years younger, respectively, than whites. In colored persons cirrhosis of the liver was encountered in 9.1% of men, and in 4.8% of women; and malignant tumors were found in 12% and 12.1%, respectively. Higher mortality from tuberculosis and syphilis and death at younger age probably account for the lower ratios.

TABLE 5.—ALL CASES OF MALIGNANT TUMOR

	Age at death, yrs.			
	20–39	40–59	60–	Total
Men without cirrhosis of liver:				
No.	49	311	382‡	742
%*	7.0	15.3	23.4	17.0±0.6
Men with cirrhosis of liver:				
No.	2†	28	47	77
%*	5.4	12.7	25.4	17.4
Women without cirrhosis of liver:				(16.3±1.7)§
No.	45	120	118	283
%*	10.7	19.25	21.1	17.4±1.0
Women with cirrhosis of liver:				
No.	..	8	15	23
%*	..	9.5	26.3	13.9
				(12.9±2.6)§

* In per cent of all examined postmortem (see Table 1).
† Both cases are colored.
‡ Among them 4 cases of unknown age.
§ Age-adjusted.

The association of cirrhosis and malignant tumor of the liver in colored men is more frequent than in whites. In 505 colored men without cirrhosis, intrahepatic malignant tumor was found only once, while in 48 with cirrhosis the combination was found 5 times. In the group of 3860 white non-cirrhotics intrahepatic tumor occurred 16 times, and in 395 white cirrhotics 13 times.

The number of colored women (15) having cirrhosis is too small to warrant generalizations. None of them developed a malignant tumor.

TABLE 6.—WHITES; MALIGNANT TUMORS IN VARIOUS GROUPS OF ORGANS PER 100

	Organs					
	Liver and intrahepatic ducts Sub 1a	Extrahepatic bile passages and pancreas Sub 1b	Mouth, pharynx, larynx, and esophagus Sub 2	Intestines from duodenum to the anus Sub 3	Inner female genital organs Sub 4	All other organs incl. hematopoietic system Sub 5
Men without* cirrhosis of liver	0.4	0.9	2.0	2.6	..	11.8
Men with† cirrhosis of liver	3.3	3.0	2.8	2.8	..	4.8
Women without‡ cirrhosis of liver	0.2	1.6	0.6	4.0	2.4	9.4
Women with§ cirrhosis of liver	1.5	3.5	..	3.5	3.0	4.7

	All organs	
	Crude	Age-adjusted
Men without* cirrhosis of liver	17.8	17.8
Men with† cirrhosis of liver	16.6	15.0
Women without‡ cirrhosis of liver	18.2	18.2
Women with§ cirrhosis of liver	16.2	15.0

* 3860 cases.
† 395 cases.
‡ 1332 cases.
§ 142 cases.

Restricting considerations to whites, one finds all the results obtained in the former analysis to be valid. In the age group 20–39 years, only

those without cirrhosis showed malignant tumors (7.6% of the men, and 10.6% of the women). In the middle age group, malignant tumors were encountered in non-cirrhotics in 15.8% (M) and 19.3% (F) respectively; and in 10.7% (M) and 11% (F) of cirrhotics. Within the highest age group, there is practically no difference in the percentage of malignant tumors between male non-cirrhotics (24%) and cirrhotics (23.3%), whereas cirrhotic women have a higher percentage of malignant tumors (27.7%) than non-cirrhotics (22.5%). The values for all age groups taken together are demonstrated in Table 6.

Early Cirrhosis and Malignant Tumors. In 1125 persons with malignant tumor, and in 5471 persons free from it, cirrhosis was found in 8.9% and 9.3% respectively. Of 42 persons with intrahepatic tumor 47.6% had cirrhosis; of 81 cases with a tumor in the extrahepatic bile passages or pancreas 22.2% had cirrhosis; and of the remaining 1002 tumor cases only 6.2% exhibited this liver condition.

Of the 100 persons who had both a malignant tumor and cirrhosis, 34% had cirrhosis in an early stage; for the 508 cirrhotics without a malignant tumor the corresponding figure is 28.3%. The difference is insignificant. Dividing, however, the formerly mentioned group of 100 cases according to the primary site of the tumor we find considerable differences as to the percentage of early cirrhosis.

Of the 20 cases of intrahepatic carcinoma combined with cirrhosis, only one example was classified as early cirrhosis; and of the 12 cirrhotics with a tumor of the mouth, pharynx, larynx and esophagus, only 2 had cirrhosis in an early stage. On the other hand, in cirrhotics with a primary tumor in extrahepatic bile passages or pancreas, 7 out of 18 had early cirrhosis. Here, of course, one may assume that the tumor led to the development of cirrhosis, and that the death occurred too early. Still larger is the portion of early cirrhosis in those who had a carcinoma or sarcoma of the intestines—7 out of 16—or a primary tumor in one of the other organs. In this latter group, out of 34 cirrhotics 17 had an early cirrhosis. The mechanism involved in obstructive biliary cirrhosis does not explain the high proportion of early cirrhosis in the latter 34 cases.

As a whole, the group of 178 cases with early cirrhosis has a ratio of malignant tumors a little higher than is that of non-cirrhotics (19.1% as compared with 17%) or the ratio of persons with fully developed cirrhosis (15.3%). There are also differences in the distribution of the tumors according to the organ.

Simultaneous Multiple Tumors. Of 1025 cases of malignant neoplasm without cirrhosis 29 (2.8%) had at least two primary tumors. In 26 of these neither the biliary system nor the pancreas was involved. The 3 other cases presented a combination of primary neoplasms in liver and stomach, in pancreas and breast, and in pancreas and kidney. Among 100 cases of malignant tumor associated with cirrhosis, multiple malignant tumors were encountered twice (2%). In one, pancreas and the prostate were the sites of carcinoma, in the other tongue and skin of the nose.

TABLE 7.—PERCENTAGE DISTRIBUTION OF THE PRIMARY TUMORS

	Organ			
	Biliary system, pancreas, mouth, pharynx, larynx, or esophagus Sub *a*	Intestines, or genital organs Sub *b*	All other organs Sub *c*	All organs
1025 persons with tumor:				
Without cirrhosis	17.8	19.8	62.4 ± 1.5	100.0
34 persons with tumor:				
With early cirrhosis . . .	29.4	29.4	41.2 ± 8.4	100.0
66 persons with tumor:				
With fully developed cirrhosis	60.6	14.9	24.5 ± 2.8	100.0

Discussion. It will be recalled (Table 6) that of 100 non-cirrhotic males 17.8% had a malignant tumor, and of 100 cirrhotic males only 16.6%. This difference is statistically insignificant. There are, however, in this table 2 groups of organs with significant differences. In one group, sub 1, cirrhotics have a higher percentage of malignant tumors, while in the other, sub 5, cirrhotics have a considerably lower percentage of tumors than non-cirrhotics (4.8% as compared with 11.8%). Since this difference is found in all 3 age groups, it is not accounted for by premature death, and has to be explained in another way.

Does the value of 4.8% indicate a real deficit in the incidence of these tumors? In other words, do 1000 cirrhotics taken at random from the general population and followed until death have an incidence of malignant tumors in these "other organs" (Table 6, sub 5) smaller than have 1000 non-cirrhotics of the same age, sex and color? The answer depends on the frequency with which cirrhosis is responsible for the death.

An example may clarify the issue. Suppose that within a certain time, of 1000 cirrhotics 80 will die free of a malignant tumor, 10 will succumb to a tumor of one of the organs enumerated in Table 6, sub 1 to 4, and 10 will die of a tumor of one of the "other organs." Let us furthermore suppose that for 1000 non-cirrhotics the corresponding values are 50, 2, and 10 respectively. Under these circumstances, the incidence of tumors of an organ listed sub 5 of Table 6 is equal for both, cirrhotics and non-cirrhotics, namely $10/1000 = 1\%$. Nevertheless, dealing only with those who died, one is likely to overlook that equality, since of 100 deaths in the cirrhotic group $\frac{10}{80 + 10 + 10} = 10\%$ were due to malignant tumors of one of the "other organs," while the corresponding figure for non-cirrhotics is higher, namely $\frac{10}{50 + 2 + 10} = 16.1\%$. In this mock example, the incidence of malignant tumors of the stomach, the kidney, the lungs, the bladder, prostate, breast, thyroid, hematopoietic system, etc., would be just as high in cirrhotics as in non-cirrhotics, although in the total of deaths of cirrhotics these malignant neoplasms occupy a smaller percentage.

Before drawing conclusions from our actual figures, two values have to be estimated. First, one has to know how much the non-cancerous

mortality of non-cirrhotics is exceeded by that of cirrhotics; secondly, how high this excess would have to be in order to make the percentages sub 5 of Table 6 compatible with an undiminished incidence of these tumors within the total group of cirrhotics in the general population.

About the first point no data exist. Cirrhotics may have a surplus mortality on account of the cirrhosis, and on account of other non-cancerous diseases complicated by cirrhosis. In our postmortem series, 9.2% had cirrhosis, while in the Metropolitan Life Insurance statistics of causes of death[1] the corresponding figure is but one-seventh of this percentage. This indicates for cirrhotics an excess mortality due to cirrhosis of approximately 14%. The excess mortality due to the aggravation of other diseases cannot be calculated at all; only guessing is possible. Furthermore, in the general population the percentage of cirrhotics, especially of those with a fully developed cirrhosis may be somewhat smaller than in the postmortem series. These two factors, just mentioned, may account for an increase of the above calculated figure of 14% to about twice that value, or even a little more. This is a rough estimate.

On the other hand, we are able to calculate that the mortality of cirrhotics of all age groups would have to exceed that of non-cirrhotics by at least 82% in men, and 62% in women, in order to make the diminished ratio of tumors in "other organs" (see Table 6, sub 5) compatible with an undiminished incidence of these tumors per 1000 cirrhotics in the total population. Within the age groups of 20–59 years the discrepancy would be much larger. Furthermore one should bear in mind that the changes in the distribution of malignant tumors by site and the diminished ratio of tumors in the "other organs" are not limited to the fully developed cases of cirrhosis. We found them also in the group of 178 cases of early cirrhosis (Table 7), where this disease hardly is causing any excess mortality.

Thus we arrive at the conclusion that in cirrhotics the incidence of tumors in the stomach, kidney, bladder and prostate, lungs, breast, thyroid, hematopoietic tissue, etc., is lower than in non-cirrhotics. It is a real deficit, due to the increased frequency of malignant tumors in other organs in cirrhotics. This finding is in keeping with our results obtained in the analysis of other carcinogenic factors, regardless whether they do, or do not, deteriorate general health.[6,7]

Summary and Conclusions. 1. In necropsy records of 6596 persons over 20 years of age, cirrhosis of the liver was found in 9%, and malignant tumors in 17%. About 30% of cirrhosis were classified as "early."

2. Compared with non-cirrhotics, persons with cirrhosis have a ratio of intrahepatic tumors several times increased; the ratio of malignant tumors in extrahepatic bile passages and pancreas increased to a smaller degree. Furthermore, male cirrhotics showed an increased ratio of malignant tumors of the mouth, pharynx, larynx and esophagus.

3. Cirrhotics have a much lower ratio of malignant tumors of all other organs taken together. The degree to which the ratio of tumors of all these "other organs" is diminished varies inversely with age.

4. Though increased general mortality is involved in bringing out

findings of paragraph 3, the second reason for the low ratio of malignant tumors of "all other organs" in cirrhotics is the actually diminished incidence of malignant tumors in this large group of organs. This is in keeping with our former investigations on the rôle of chronic irritation in human cancer.

5. Thus if by dietary or other measures cirrhosis of the liver could be prevented, the organ distribution of malignant tumors in human beings would change, but the total incidence of cancer scarcely would be reduced.

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A CASE OF TOOTHPICK PERFORATION OF THE INTESTINES

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Intestinal perforation by an ingested sharp foreign body seems to occur more commonly than the literature indicates.[1] McManus[3] in 1941 was able to collect but 93 cases to which he added 2 of his own. He divided the perforating foreign bodies into 3 general groups: metallic bodies, 45 cases; animal bone, 39 cases; wood splinters, 9 cases. Included in the last group were several perforations due to a swallowed toothpick. Because of the rarity of perforation by such a commonly used object, the report of an additional case seems to be in order.

Case Report. W. L., a 63-year-old colored male, entered this hospital October 29, 1941, complaining of abdominal pain. He had been in good health until 10 days earlier when he noticed periodic cramp-like pain about his umbilicus. The pain was annoying but not disabling until 48 hours before admission when it became constant, more severe, and generalized. He then became nauseated and vomited; the pain and vomiting continued. His bowels had been normal. He had had no previous gastric symptoms. Except for lobar pneumonia in 1930, the past history was essentially negative. Physical examination revealed a slender male in acute distress, perspiring freely. The temperature was 100° F.; the pulse regular, 80 per minute; respiratory rate, 30. Significant findings were confined to a moderately distended and extremely tender abdomen. Maximum tenderness lay between the umbilicus and the symphysis. Rebound pain was marked. Peristalsis was absent. Roentgen examination on admission showed a small dilated loop of ileum in the right lower abdomen but no free air. The leukocyte count was 16,300 per c.mm. The red blood cell and hemoglobin determinations, blood chemistry values, and urinalysis were all within normal limits. The Kahn test was negative.

On conservative therapy, the patient's condition improved rapidly in the next 4 days during which time a grapefruit sized mass fixed to the abdominal wall developed in the lower mid-abdomen. Roentgen examination by barium enema showed a ptosed transverse colon adherent to the anterior abdominal wall at the site of the palpable mass. Incision and drainage was performed 12 days after admission and several ounces of thin purulent material were removed. The mass gradually decreased in size, while a small amount of drainage persisted. Intermittently, the patient gave evidence of partial small bowel obstruction. The appendix was at this time visualized by Roentgen examination as distinct from the mass. At operation under spinal anesthesia 36 days after admission, the abdominal wall sinus was found to communicate with an inflammatory mass the size of a hen's egg one end of which was connected to the mid-portion of the transverse colon, while the other end was connected to a loop of ileum adherent to the anterior abdominal wall just above the bladder, resulting in marked angulation of the bowel. This mass proved to be a foreign body granuloma containing a toothpick. Though it could not be definitely established, it was felt more likely from the findings that the toothpick had first penetrated the transverse colon and that the ileum had later impaled upon the toothpick. After excision of the mass, repair of the bowel walls and implantation of sulfanilamide in the abdominal cavity, the abdominal wall was closed. The patient was discharged 15 days post-operatively as cured. At no time could he recall having swallowed the toothpick, an interesting observation noted by others.[2,3]

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STUDIES ON PROTHROMBIN

II. The Effects of a Single Small Dose of Dicumarol* (3, 3′ Methylenebis [4-Hydroxycoumarin]) in Liver Disease

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It has been observed that the same dose of Dicumarol (3, 3′ methylenebis (4-hydroxycoumarin)) administered to different individuals may induce varying degrees of hypoprothrombinemia.[2,3] Studies were undertaken to determine what might be the factors responsible for this variation.

As far as is known, Dicumarol acts chiefly on the prothrombin level (or activity).[1] That the liver plays an essential rôle in the elaboration

* Dicumarol is the collective trademark of the Wisconsin Alumni Research Foundation, which controls the use thereof.

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of prothrombin has been established.[5] It appeared of interest, therefore, to investigate the reaction to Dicumarol of patients with liver disease.

The minimal single dose required to induce prolongation of the prothrombin time in 20 normal individuals was found to be 100 mg. It was decided to administer single doses of 50 mg. to a group of patients with liver disease. Sixteen were cases of Laennec's cirrhosis of the liver, one acute hepatitis, and one Wilson's disease.

TABLE 1.—EFFECT OF DICUMAROL ON PROTHROMBIN

Case No.	Initial prothrombin times: Whole plasma (sec.)	Initial prothrombin times: 12.5% plasma (sec.)	Initial prolongation	Maximal prothrombin times after 50 mg. Dicumarol: Whole plasma (sec.)	Maximal prothrombin times after 50 mg. Dicumarol: 12.5% plasma (sec.)	Response	Remarks
1	22.5	82.0	Marked	24.5	96.0	Pos.	History of spontaneous hemorrhages
2	20.0	78.0	Mod.	21.8	90.0	Pos.	
3	27.6	61.0	Mod.	29.0	76.0	Pos.	Brain thromboplastin used
4	19.0	60.0	Mod.	21.5	68.0	Pos.	Dicumarol given intravenously
5	18.2	62.0	Mod.	24.0	76.0	Pos.	
6	17.0	48.0	Sl.	17.2	59.1	Pos.	
7	14.0	52.0	Sl.	14.2	59.0	Pos.	
8	16.9	60.0	Mod.	18.4	76.0	Pos.	
9	17.0	44.5	Nor. (?)	16.8	41.5	Neg.	
10	15.0	42.5	Nor. (?)	16.8	42.5	Neg.	
11	17.6	49.5	Sl.	18.0	50.2	Neg.	
12	17.0	58.0	Sl.	17.1	59.9	Neg.	
13	17.2	44.2	Nor. (?)	16.8	45.5	Neg.	
14	15.4	46.0	Nor. (?)	16.5	48.6	Neg.	Dicumarol given intravenously
15	15.8	47.7	Sl.	17.9	48.2	Neg.	Dicumarol given intravenously
16	15.1	60.0	Mod.	14.2	61.1	Neg.	Wilson's disease
17	15.4	45.2	Nor. (?)	15.5	45.0	Neg.	Dicumarol given intravenously
18	14.7	54.0	Sl.	17.0	72.0	Pos.	Acute hepatitis

NOTE: Lung thromboplastin used in all cases except Case No. 3.

Normal Standards

RABBIT LUNG THROMBOPLASTIN

Whole Plasma: Arithmetic Mean 15 sec.; Standard Deviation ±2

12.5% *Plasma*: Arithmetic Mean 39.5 sec.; Standard Deviation ±2.5

RABBIT BRAIN THROMBOPLASTIN

Whole Plasma: Arithmetic Mean 24 sec.; Standard Deviation ±2.3

12.5% *Plasma*: Arithmetic Mean 41.4 sec.; Standard Deviation ±3.8

TABLE 2.—BLOOD VALUES BEFORE AND DURING RESPONSE TO DICUMAROL

	Preëxisting values					Values during response to Dicumarol				
		Plasma, prothrombin time		Serum proteins, gm. per 100 ml.			Plasma, prothrombin time		Serum proteins, gm. per 100 ml.	
Case No.	Date	Whole (sec.)	12.5% (sec.)	Total	Albumin	Date	Whole (sec.)	12.5% (sec.)	Total	Albumin
2	5/16	20.0	78	6.81	4.52	5/19	21.8	90	6.95	4.56
3	5/16	27.6	61	6.07	4.08	5/19	29.0	76	5.98	4.22
5	5/16	18.2	62	6.14	3.04	5/19	24.0	76	6.80	3.27

Procedure. The method used for prothrombin estimation has been described by us.[4] In this procedure, the prothrombin time of both whole and diluted (12.5%) plasma are estimated in duplicate.

Several prothrombin estimations were made in each case before the Dicumarol was administered, to establish the resting value for the prothrombin time of each subject. Fifty mg. of Dicumarol were then given either intravenously (4 cases) or orally. Blood samples were taken after 6, 12, 24 and 48 hours. In 7 cases additional specimens were obtained after 18 hours, and in 4 of these after 72 hours. The maximum prothrombin times obtained are recorded in Table 1.

The total serum proteins and albumin-globulin ratio were determined in Cases 2, 3 and 5 before and during the interval when the prothrombin time was prolonged after Dicumarol (Table 2).

Discussion of Results. The mechanism whereby Dicumarol influences prothrombin is still obscure. In view of the importance of the liver in the elaboration of prothrombin, increased reactivity to Dicumarol in cases with hepatic functional derangement is significant.

Only 4 of the cases with liver disease showed prolongation of the whole plasma prothrombin time, while 7 showed a marked or moderate* prolongation of the diluted (12.5%) plasma prothrombin times and 6 cases showed a slight prolongation of the diluted plasma prothrombin time.

The prolongation of the preëxisting plasma prothrombin time is tentatively considered as a measure of the insufficiency of the prothrombin elaborating function of the cirrhotic liver. Consequently, the 5 cases showing normal prothrombin times will be considered as having normal liver function in respect to prothrombin elaboration and reactivity to Dicumarol.

All of the cases of cirrhosis of the liver and the single case of acute hepatitis, which showed an initial marked or moderate prolongation in the diluted plasma prothrombin time showed a definite response to 50 mg. of Dicumarol. Of the 6 cases which showed a slight prolongation of the diluted plasma prothrombin time, 3 responded to 50 mg. of Dicumarol. Cases with normal prothrombin time did not respond to this small amount of Dicumarol, nor did the 1 case of Wilson's disease, although the initial diluted plasma prothrombin time was moderately prolonged. It appears unprofitable therefore, to pursue the investigation further as a measure of the functional capacity of chronic cases of Laennec's cirrhosis of the liver.

As noted above, we have found that the prothrombin times of normal individuals does not increase after the administration of a single dose of 50 mg. of Dicumarol. Consequently, this investigation indicates that in Laennec's cirrhosis the subject responds to smaller quantities of Dicumarol than does the normal individual only when the disturbance in the liver causes prolongation of the prothrombin time.

The cases of liver disease responding to 50 mg. of Dicumarol showed the first detectable prolongation of the prothrombin time in the period of 12 to 24 hours after administration of Dicumarol. The latent period is of the same duration as that experienced when normal individuals are given an effective dose of Dicumarol. The character and duration of the response obtained by feeding 50 mg. of Dicumarol to cirrhotics is similar to that observed in normals after larger doses. The response usually involves a latent period followed by periods of depletion, plateau, and finally, restoration to the initial prothrombin time.

* Marked prolongation = Diluted plasma prothrombin time approximately twice normal.
Moderate prolongation = Diluted plasma prothrombin time between approximately 1½ and twice normal.
Slight prolongation = Diluted plasma prothrombin time less than 1½ times normal.

The total serum proteins and the A/G ratio were not measurably altered during the interval when the hypoprothrombinemic effect of Dicumarol was manifest.

The data presented here are significant in the therapeutic application of Dicumarol. It is fundamental that the prothrombin time be determined before the dosage of the anticoagulant is outlined. It appears also that the greater sensitivity of the method used here for the estimation of prothrombin time, makes it preferable to those in which only whole plasma is examined.

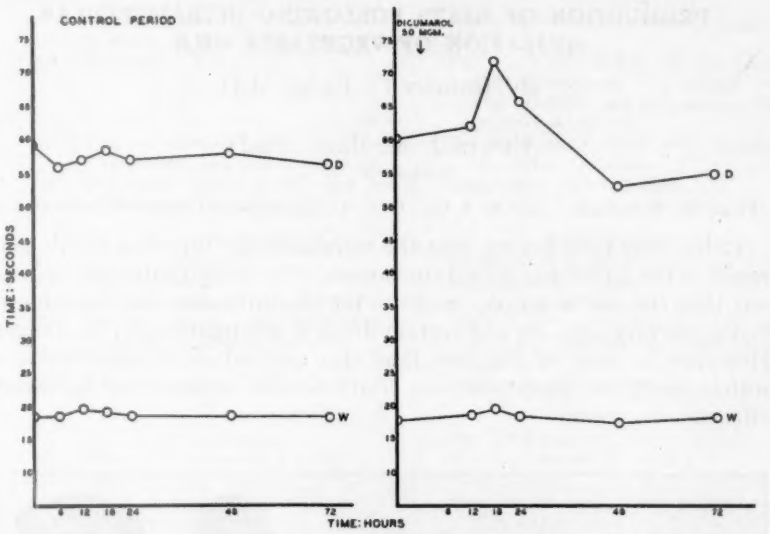

CHART 1.—Prolongation of diluted (12.5%) plasma prothrombin time after 50 mg. Dicumarol. The whole plasma prothrombin time is unaltered. Note overcompensation after prolongation.

Summary. Fifty mg. of Dicumarol (3, 3′ methylenebis (4-hydroxycoumarin)), one-half the minimal dose found to induce a detectable prolongation of the prothrombin time in normal individuals, was administered to 18 patients with liver disease and with hypoprothrombinemia of varying intensities. All of the cases of Laennec's cirrhosis with marked or moderate preëxisting prolongation of the diluted plasma prothrombin time showed a definite response to the smaller dose of Dicumarol. Of 6 cases with slightly prolonged diluted plasma prothrombin time, 3 showed further increase, while no case with initial normal prothrombin time responded to the 50 mg. dose of Dicumarol. In those in which prolongation did occur the time of the first detectable change was the same as in normal individuals.

We wish to thank Dr. Arthur J. Patek, Jr., for making available to us for study several cases on the First Medical Division, Welfare Hospital. The protein determinations were done by Miss Yetta Porosowska. Miss Frances Kaufman gave technical assistance. The Dicumarol was supplied by Dr. K. K. Chen of Eli Lilly & Co. This work was aided in part by a grant from the Arlington Chemical Company, Yonkers, N. Y.

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PRODUCTION OF CYSTS FOLLOWING INTRAMUSCULAR INJECTION OF VEGETABLE OILS

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It has long been known that the intramuscular injection of oils may result in the formation of cysts or tumors.[1-7,9] Sevringhaus[8] has pointed out that the use of an oily medium for the intramuscular injection of endocrine preparations and certain drugs is not unattended by danger. However, in spite of the fact that this method of administration is widely used, the literature cites relatively few instances of untoward effects.

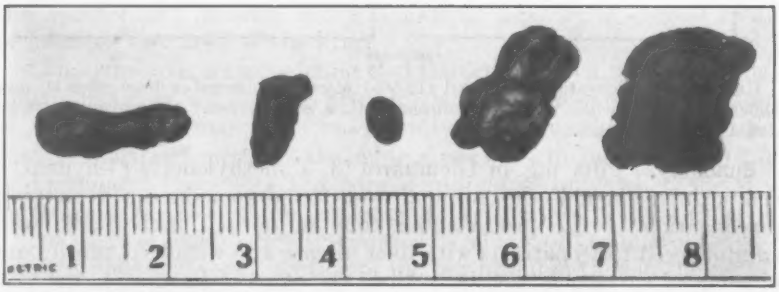

Fig. 1.—Photograph showing cysts as removed by dissection from rats following intramuscular injection of vegetable oils. From left to right the cysts are: unilocular cyst from sesame oil; multilocular cyst from corn oil; thin-walled unilocular cyst following olive oil; multilocular cyst with large amount of connective tissue following peanut oil; many small cysts in mass of tissue following injection of sesame oil and ether.

The present study was undertaken in order to determine which of a group of 5 common vegetable oils was most innocuous. The effects of reducing the viscosity of the oil by a mixture with ether was also studied.[10] The 5 oils selected were corn oil, U.S.P., cottonseed oil, U.S.P., olive oil, U.S.P., sesame oil, U.S.P., and 2 samples of high grade peanut oil. A series of oil-ether solutions was also prepared by mixing 6 parts of the oil with 4 parts of diethyl ether, U.S.P.

Methods. All of the solutions to be injected were sealed in ampules and autoclaved at 15 lbs. pressure for 20 minutes. The oils were injected into the muscles of the right thigh of adult albino rats. The corresponding oil-ether solution was injected into the left thigh. All doses were 0.5 cc. Five animals were used for each kind of oil, except that only 2 were used with peanut oil (B). Altogether a total of 27 rats were used, each receiving 2 injections. One animal of each group was killed and autopsied at the following time intervals after injection: 4, 11, 18, 25, 32, and 40 days.

TABLE 1.—APPEARANCE OF CYSTS AT VARIOUS INTERVALS AFTER INJECTION OF FIVE OILS WITH AND WITHOUT ETHER

Days elapsed after injection	Corn oil	Corn oil and ether
11	Several multiloc. (4 mm.)*	Many multiloc., thin walls (1–2 mm.)
18	One large (4 mm.), many sm. (1 mm.)	Few sm. (1 mm.)
25	Multiple (1–5 mm.)	Sev. (1–2 mm.); soft fat-like tissue around injection site; inflam. fat with necrosis and perivascular deposition of calcium
32	Few sm. cysts (1 mm.); thick walls; mod. amt. chr. inflam. reaction	Sev. (2–4 mm.); thick walls; marked chr. inflam. reaction
40	One large (5 mm.); sev. sm. cysts (1 mm.)	Three thin-walled (1 mm.)
	Cottonseed oil	**Cottonseed oil and ether**
11	None; oil in muscle	None; oil in muscle
18	None; oil in muscle	Sm. multiple (1 mm.)
25	Many (1–4 mm.)	Many (1 mm.)
32	One large (6 mm.); sev. small (1 mm.); eos. in intercystic tissue	Several large (2–3 mm.); many sm. (1 mm.); marked chr. inflam. reaction
40	One (4 mm.); sev. (1 mm.)	Many sm. adj. (1 mm.)
	Olive oil	**Olive oil and ether**
11	Sev. multiloc. (1 mm.)	Sev. (2–4 mm.)
18	Many thin-walled (2–4 mm.)	Few thin-walled (1–3 mm.)
25	Mult. sm. (1–2 mm.)	Few (1 mm.)
32	Mult. (1–1.5 mm.)	Few sm. (1 mm.); widely separated; thin walls
40	One ovoid (2 x 2 x 3 mm); thick walls	Many (1 mm.)
	Sesame oil	**Sesame oil and ether**
11	Sev. multiloc. (2–4 mm.)	None; oil in muscle
18	Mult. (2–4 mm.)	Many thin-walled (1–3 mm.)
25	Several large (2–4 mm.)	Many sm. (1–2 mm.)
32	One large (6 mm.); few sm. (1 mm.)	Many sm. (1 mm.); marked chr. inflam. reaction
40	Several (3 mm.)	No oil found
	Peanut oil (A)†	**Peanut oil (A) and ether**
11	Sev. multiloc. (2–4 mm.)	None; oil in muscle
18	Many thin-walled (2–4 mm.)	Few thin-walled (1–3 mm.)
25	Sev. sm. thin-walled	Sev. (2–4 mm.)
32	Mult. sm. thin-walled (1–1.5 mm.)	None
40	One (1 mm.)	Four (1–2 mm.)
	Peanut oil (B)†	**Peanut oil (B) and ether**
7	Three (1.5–3 mm.)	One large intramusc. septa
21	Two large (4–5 mm.); sev. adjacent (1 mm.); fatty tissue adjacent	Sev. sm., multiloc. (1 mm.)

* Dimensions expressed in mm. (millimeter) refer to the average approximate diameter of the cysts.

† Two different samples of peanut oil were used.

Results. Translucent cysts filled with oil were generally formed by all 5 oils and by all of the oil-ether solutions (Table 1). In number

and size they ranged from many small, thin-walled cysts to 1 or 2 cysts as large as 6 mm. in diameter (Fig. 1). In only 7 out of 54 possibilities were no cysts found. In the 7 scattered instances in which oil but no cysts were found, the cysts may have been broken during dissection since they were generally thin-walled and quite fragile. These experiments indicate that there is little choice among these oils; all appear to produce similar cysts with equal frequency in rats.

As the experiment progressed no increases or decreases in the size, number or appearance of the cysts were observed.

Discussion. The oil-ether solutions produced less intercystic tissue, smaller cysts and in general the cyst walls were thinner. The oil-ether solutions also possessed the practical advantage of being much easier to inject. This was probably due to their lower viscosity. Since the total volume of oil and of the oil-ether solution injected was the same in each case (0.5 cc.) the actual amount of oil given in the oil-ether mixture was less. It seems doubtful that this fact would have any bearing on the results.

Summary. Cysts generally resulted from the intramuscular injection of the following vegetable oils: corn oil, cottonseed oil, olive oil, sesame oil and peanut oil and of oil-ether solutions in rats.

No indications were found that cysts became progressively smaller or larger, or changed in number or appearance with time.

No one oil appeared to be outstandingly better or worse than another oil in so far as cyst production was concerned.

The addition of ether to oil made injections easier and possibly decreased damage to the tissue.

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GALLOP RHYTHM—INCIDENCE AND THE INFLUENCE OF AGE, RACE AND SEX

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Gallop rhythm is a disorder of the heart beat characterized by the occurrence of 3 heart sounds during each cardiac cycle. Systolic gallop, in which the third sound occurs in systole, is rare and apparently

not of much clinical importance. Diastolic gallop rhythm, although not defined exactly the same way by all cardiologists, is considered uniformly to be of great clinical significance. It is with this type of gallop rhythm that this paper deals.

This study of gallop rhythm is based upon the clinical and pathologic records of 790 consecutive, adult patients who died of heart disease. These cases occurred in 6548 consecutive postmortem examinations done at Cleveland City Hospital in the decade from January, 1930, to December, 1939, inclusive. Gallop rhythm was present in 199 patients. The diagnosis of gallop rhythm was made clinically and was corroborated by phonocardiography only exceptionally.

The majority of the gallops seemed to be of the variety considered to be due to auricular contraction. In only 2 of the 199 patients with gallop rhythm was auricular fibrillation present. In these 2 cases the gallop presumably was due to a third heart sound, and no doubt in a few more instances this was the etiology of the gallop, although such cases appeared to be in the minority.

Discussion. *The Incidence of Gallop Rhythm in Various Types of Heart Disease.* Wolferth and Margolies[2] wrote that there were no quantitative data available as to the clinical incidence of gallop rhythm. They declared that there was no doubt that myocardial damage, both acute and chronic, predisposed to the development of gallop sounds. They considered that gallop occurred particularly in active rheumatic carditis, coronary occlusion, hypertensive cardiovascular disease, hyperthyroidism and anemia, and that it was very uncommon in patients with mitral stenosis.

The incidence of gallop rhythm in the various types of heart disease is shown in Table 1. It is seen that gallop rhythm occurs most frequently in hypertensive heart disease and coronary artery disease; 1 out of every 3 patients had this type of rhythm. Cor pulmonale was associated with gallop rhythm in about 1 case in 5. Only 1 of 10 patients who died of rheumatic heart disease or syphilitic heart disease had gallop rhythm.

TABLE 1.—THE FREQUENCY DISTRIBUTION OF GALLOP RHYTHM IN THE VARIOUS TYPES OF HEART DISEASE

Type of heart disease	No. of cases	No. with gallop rhythm	%
Hypertensive heart disease	264	93	35.2
Coronary heart disease	177	55	31.1
Rheumatic heart disease	119	12	10.1
Syphilitic heart disease	67	7	10.4
Cor pulmonale	54	10	18.5
Subacute bacterial endocarditis	31	2	6.4
Acute bacterial endocarditis	13	1	7.7
Thyroid heart disease	9	1	11.1
Calcific aortic stenosis	9	3	33.3
Obliterative pericarditis	7	0	0.0
Tuberculous pericarditis	7	4	57.1
Miscellaneous	14	3	21.4
Undiagnosed	19	8	42.1
	790	199	25.2

In relation to rheumatic heart disease, it is generally thought that gallop rhythm may readily occur in patients with active rheumatic carditis but that it is extremely rare in patients with well-developed mitral stenosis.[2] This idea is supported by this study. Of the 119 patients dying of rheumatic heart disease, 12 showed a gallop rhythm. Five of these 12 patients had acute rheumatic pancarditis. The remaining 7 showed various degrees and combinations of chronic rheumatic endocarditis, but in only 2 was there stenosis of the mitral valve (the entire series included 82 instances of mitral stenosis).

One of these patients with mitral stenosis and gallop rhythm was a 59-year-old white man who had severe arteriosclerosis of the coronary arteries with fibrosis of the myocardium. Coronary disease may have been a factor in the production of gallop rhythm in this case. The other was a 35-year-old colored female whose heart showed chronic rheumatic valvulitis of the mitral, tricuspid and aortic valves with stenosis of the mitral and tricuspid valves. No other explanation than the rheumatic heart disease was found to account for the gallop which had been heard by a number of observers.

In the other common type of valvular heart disease, syphilitic heart disease, gallop rhythm likewise is considered to occur uncommonly. In this study, of the 67 persons who died of syphilitic heart disease, 7 had gallop rhythm. But of these, 1 had complicating hypertensive heart disease, and 2 had complicating coronary artery disease (1 with recent myocardial infarction). In only 4 cases was there apparently no other explanation for the gallop than the syphilitic heart disease.

TABLE 2.—THE FREQUENCY DISTRIBUTION OF DEATHS OF PATIENTS FROM, 1, HYPERTENSIVE HEART DISEASE WITH GALLOP RHYTHM AND, 2, HYPERTENSIVE HEART DISEASE WITHOUT GALLOP RHYTHM

Age (yrs.)	Hypertensive heart disease with gallop rhythm	Hypertensive heart disease without gallop rhythm	Total
15–19	1	..	1
20–24	1	..	1
25–29	2	..	2
30–34	10	2	12
35–39	11	4	15
40–44	8	13	21
45–49	10	19	29
50–54	18	24	42
55–59	11	33	44
60–64	11	21	32
65–69	7	28	35
70–74	3	14	17
75–79	..	11	11
80–84	..	2	2
	93	171	264

Relationship of Age and Gallop Rhythm. The age in years at death of the patients who had hypertensive heart disease with and without gallop rhythm appears in Table 2. The average age at death of the patients with gallop rhythm was 49.5 years, the standard error being ±1.3. The average age at death of the patients without gallop rhythm

was 58.8 years (standard error ±0.8). The standard error of the difference between these two averages is 1.5. The actual difference, 9.3 years, is 6.2 times this standard error, an indication that the difference is a highly significant one. It appears that it can be concluded that in fatal hypertensive heart disease, gallop rhythm is found in younger patients.

The age in years at death of the 55 patients with coronary heart disease and gallop rhythm, and the 122 patients without gallop rhythm appears in Table 3. The average for those with gallop rhythm was 57.3 years (standard error ±1.4). For those without gallop rhythm it was 64.4 years (standard error ±1.0). The standard error of the difference between these two averages is 1.8. The actual difference, 7.1 years, is 4.0 times this standard error, an indication that the difference is a highly significant one. Accordingly, it would seem that, on the average, in fatal coronary heart disease, patients with gallop rhythm are apt to be younger than those without gallop rhythm.

TABLE 3.—THE FREQUENCY DISTRIBUTION OF DEATHS FROM, 1, CORONARY HEART DISEASE WITH GALLOP RHYTHM AND, 2, CORONARY HEART DISEASE WITHOUT GALLOP RHYTHM

Age (yrs.)	Coronary heart disease with gallop rhythm	Coronary heart disease without gallop rhythm	Total
30–34	1	1	2
35–39	2	2	4
40–44	4	4	8
45–49	7	9	16
50–54	7	8	15
55–59	13	21	34
60–64	7	9	16
65–69	8	28	36
70–74	5	17	22
75–79	..	13	13
80–84	..	8	8
85–89	1	2	3
	55	122	177

The rarity of the simultaneous occurrence of gallop rhythm and auricular fibrillation (2 in 199 cases) has been noted. This means that the patients without gallop rhythm included almost all of the persons with auricular fibrillation. There is evidence[1] that the average age at death of cardiac patients with auricular fibrillation is greater than the average age at death of cardiac patients with a normal cardiac mechanism. This raises the question as to whether patients with gallop rhythm are younger merely because the control group contains so many persons with auricular fibrillation—persons who are apt to be older. Hence it seems advisable to compare the age of patients with and without gallop rhythm, but exclusive of those with auricular fibrillation.

The average age at death of 92 patients with hypertensive heart disease and gallop rhythm but without auricular fibrillation was 49.5 years (standard error ±1.3). The average age at death of 115 patients with hypertensive heart disease and without both gallop rhythm and auricular fibrillation was 56.7 years (standard error ±1.0). The stand-

ard error of the difference between these two averages is 1.6. The actual difference, 7.2 years, is 4.5 times this standard error, an indication that the difference is a highly significant one. It appears that it can be concluded that in fatal hypertensive heart disease, even excluding patients with auricular fibrillation, gallop rhythm is found in younger patients.

The age in years at death of the 54 patients with coronary heart disease and gallop rhythm but without auricular fibrillation was 57.4 years (standard error ±1.4). For the 88 patients with coronary heart disease without both gallop rhythm and auricular fibrillation it was 62.2 years (standard error ±1.2). The standard error of the difference of these two averages is 1.9. The actual difference, 4.8 years, is 2.5 times this standard error, an indication that the difference is significant. Accordingly it would seem that in fatal coronary heart disease, patients with gallop rhythm are apt to be younger than those without gallop rhythm, even excluding patients with auricular fibrillation.

Relationship of Race to Gallop Rhythm. The 264 patients with hypertensive heart disease consisted of 168 white and 96 colored patients. Of the 168 white patients, 53 (31.5%) showed a gallop; of the 96 colored patients, 40 (41.7%) had a gallop. Although the colored patients show a higher incidence of gallop rhythm than the white patients, the difference is not statistically significant.

There were 158 white and 19 colored patients who died of coronary heart disease. The 158 white patients included 47 (29.7%) with gallop, the 19 colored patients 8 (42.1%) with gallop. Again, the incidence of gallop rhythm is higher among the colored patients, but the difference is not statistically significant.

If the patients with hypertensive and coronary heart disease are grouped together (and it must be granted that the two types of heart disease not infrequently are associated), then of the 326 white patients, 100 (30.7%) had a gallop, while of the 115 colored patients, 48 (41.7%) had a gallop. This difference is found to be significant,* and it would appear that colored patients with hypertensive heart disease and/or coronary heart disease show a higher incidence of gallop rhythm than do white patients.

Relationship of Sex to Gallop Rhythm. The 264 patients who died primarily of hypertensive heart disease included 178 males and 86 females. Of the 178 males, 62 (34.8%) had a gallop, while of the 86 females, 31 (36.0%) had a gallop. The difference is not significant when tested by the chi square method.

There were 140 males and 37 females who died of coronary heart disease. Of the 140 males, 43 (30.7%) had a gallop; of the 37 females, 12 (32.4%) had a gallop, a difference which is not significant.

Apparently there is no relationship between sex and the occurrence of gallop rhythm.

* The term "significant" refers to a difference which could be produced by chance in less than 5% of trials as demonstrated by the chi square test.

Comment. An increased frequency of occurrence of gallop rhythm in younger patients, and colored patients has been demonstrated. The association between gallop rhythm and age is marked. The relationship between gallop and colored patients could be demonstrated only by combining the hypertensive and coronary groups.

It seems likely that the association between gallop and color is really a manifestation of the influence of age. In the hypertensive group, the average age at death of the white patients was 57 years, of the colored 50. In the coronary heart group, the average age at death of the white patients was 62.6 years, of the colored patients 53.9. Thus it is seen that in both groups the white patients were older. If white and colored patients of the same age grouping are compared, no association between gallop and color is demonstrable, although the groups are not sizable.

In regard to age, however, the relationship is definite and certainly not related to color. Thus, for example, in the hypertensive group, in the group of white patients only, a higher incidence of gallop in the younger patients is easily demonstrable.

Summary. Of 790 consecutive, adult autopsied patients dead of heart disease, 199 (25.2%) had had a gallop rhythm due either to auricular contraction or a third heart sound. Gallop rhythm occurred most frequently in hypertensive heart disease and coronary artery disease; 1 out of every 3 patients had this type of rhythm. Cor pulmonale was associated with gallop rhythm in about 1 case in 5. Only 1 of 10 patients who died of rheumatic heart disease or syphilitic heart disease had gallop rhythm.

The average age at death of 93 patients with hypertensive heart disease and gallop rhythm was 49.5 years, of 171 patients with hypertensive heart disease and no gallop rhythm 58.8 years. Patients with coronary artery disease and gallop rhythm (55) averaged 57.3 years at death; 122 patients with coronary heart disease and no gallop rhythm averaged 64.4 years. Both of these differences seem to be statistically highly significant. Even if patients with auricular fibrillation are excluded (such patients rarely have gallop rhythm and are apt to be older), it still appears that the average age at death of cardiac patients with gallop rhythm is less than the average age of cardiac patients without gallop rhythm.

If the patients with hypertensive and/or coronary heart disease are grouped together, of 326 white patients, 100 (30.7%) had a gallop while of the 115 colored patients, 48 (41.7%) had a gallop. This seems to indicate that colored patients with fatal hypertensive heart disease and/or coronary heart disease, show a higher incidence of gallop rhythm than white patients. It is thought that this is really a manifestation of the influence of age, for the average age at death of the colored patients was less than that of the white patients.

No association between gallop rhythm and sex was demonstrable.

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STUDIES ON THE EFFECT AND MECHANISM OF AMPHETAMINE SULFATE ON WEIGHT REDUCTION*

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In a previous communication, one of us described the use of amphetamine sulfate in the management of obese children and was impressed by the frequent suppression of appetite following the administration of varying doses of this drug.[4]

It is our feeling that this effect could not be attributed principally to suggestion, fear of the doctor or parent, or education and suggestion during regular clinic attendance, for the following reasons: Previous medication, including thyroid extract, ephedrine, etc., had failed to affect the appetite. (In many instances there was a return of appetite and gain in weight during substitution therapy with placebos or other drugs.) Parents were instructed not to nag or police the children but to use an attitude of indifference. In a later group a prescribed reducing diet was not used, the children being permitted to eat *ad libidum* and yet, during amphetamine therapy, appetite was reduced and weight loss resulted in most instances.

We have found that many children developed a rapid tolerance to the drug. Following initial weight loss on a given dose of amphetamine, appetite returned gradually, necessitating an increase in the dose. The increased dose usually resulted in a renewed depression of appetite and loss of weight. The failure to realize this fact may account for the poor results of others.

The mechanism for the loss of appetite and decrease in weight following the use of amphetamine sulfate is still obscure. Observations from our own and from other laboratories have shown that the drug inhibits motility and emptying of the normal human and dog's stomach.[1,7] Apparently no studies on the effect of the drug on the normal hunger motility of the human stomach have been made. The effect of amphetamine sulfate on gastric secretion has been described as slight, insignificant, inconstant,[8] and significant.[6] No studies of the effects of amphetamine on psychic secretion were found in the literature. It is our purpose in this paper to present our clinical impressions and laboratory observations on the mechanism of action of this drug.

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It has been our clinical impression that under the influence of amphetamine sulfate, many of the children were more alert and exhibited greater physical activity, factors which in themselves could account for loss in weight. Recent observations have shown that the basal metabolic rate is not significantly increased by this drug.[4]

Another important feature is the ability of obese children treated with amphetamine sulfate to adhere to their diet with greater ease. Will-power seems to be definitely increased. This may be related to the effects of the drug on personality, on depressive and other abnormal mental states, on perversions of appetite, and on the emotional condition described by Lesses and Myerson as *anhedonia*.[5]* We do not feel therefore, that favorable results obtained with such different methods as drug therapy on one hand and education, suggestion and psychiatry on the other, prove that the effects of drug therapy are due to the suggestions, education, etc., which is necessarily involved in regular clinic attendance. Amphetamine renders the patient more apt to external (self) discipline. The drug may be even more useful in a class of patients in whom psychiatric treatment can be detrimental.[2]

Methods. The studies on psychic secretion were carried out on dogs provided with a double-barreled esophagostomy and with a Pavlov pouch. The animals were shamfed with ground raw meat and water, and their secretion determined during and following this procedure. Then the animals were rested and, after a period of time, amphetamine sulfate was injected and the procedure of shamfeeding was repeated. In control experiments both tests gave similar values for volume and acidity.

Gastric secretion was studied in Pavlov pouch dogs, using the double histamine test. The drug was administered at the time of the second injection of histamine.

Gastric motility was studied with the stomach balloon method, using an oil-carbon tetrachloride (sp. gr. 1.5) manometer. In the human, a moderate degree of air inflation was employed and the normal, periodic hunger motility recorded. In the dog, the stomach balloon was distended to a degree which did not produce vomiting or discomfort of the animal. This distention was productive of continuous and vigorous gastric motility, which was useful and practical for the assay of the drug.

In all series of tests, controls were performed in which nothing, water or saline solution, was administered instead of amphetamine. No appreciable effects of the water or of the saline solution were noted.

Results. *A. Psychic Secretion* (2 animals). Chart 1 represents a typical experiment. Three and 5 mg. of amphetamine sulfate injected intravenously before the second shamfeeding did not materially affect the secretion of the Pavlov pouch. Larger doses of the drug could not be employed, because the animals lost their desire to eat readily.

B. Secretion of the Pavlov Pouch (3 animals). In the double histamine test, the effects of amphetamine sulfate were variable. In some experiments secretion was increased during the first 60 minutes, but in others there was no effect. The outstanding observation in these experiments was that the effect of amphetamine sulfate, if any, was transient. In positive experiments secretion reached its peak 60 minutes after

* For reference on this and other effects of amphetamine the reader is referred to the extensive *Survey of the Literature* published by Smith, Kline & French.

injection of amphetamine and the effect of the drug had completely disappeared at the end of 90 minutes. The total acid expressed in mg. of HCL was increased considerably in some experiments while in others there was no increase, although the curve showed a distinct rise 60 minutes after injection. This latter phenomenon was due to lower values before and after the peak.

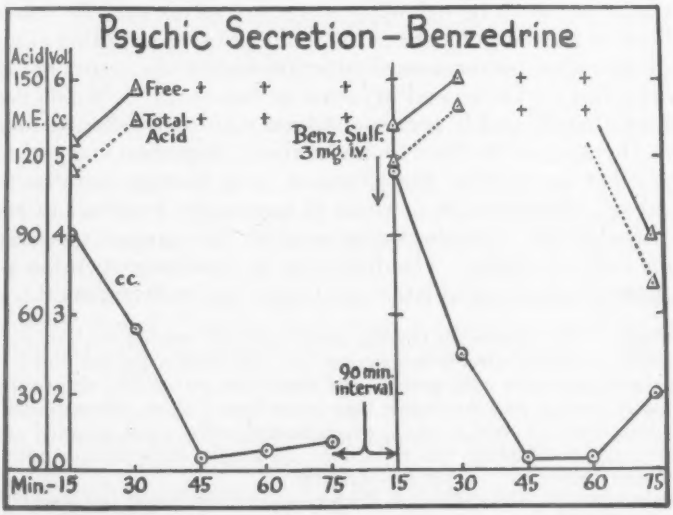

CHART 1.—Dog Lamar, 17.1 kg., male. 1-29-42. Amphetamine sulfate i.v. 30 minutes before second shamfeeding. The + signs indicate the presence of acid, but the volumes were too small for titration.

FIG. 1.—Dog. Unanesthetized, male, 10.6 kg. Continuous gastric motility from overdistention of stomach balloon. At arrow, 5 mg. of amphetamine sulfate in 5 cc. of warm water administered intraduodenally through a thin catheter, introduced through the gastrostomy cannula. After a latent period of 20 minutes motility was practically abolished for 30 minutes and greatly diminished for another 45 minutes. The dose of 5 mg. would correspond to a dose of 25 mg. in a person weighing 57 kg. (125 lbs.). Time is marked in 15 and 30 minute periods.

C. Gastric Motility (4 animals, Figs. 1 and 2; 2 human subjects, Fig. 3). In the dog small doses of amphetamine sulfate, comparable to those given to the human, suppressed motility for considerable

periods of time. Figure 1 represents a typical experiment. Figure 2 represents an atypical experiment of considerable interest. While in the typical tests a depression of gastric motility was followed by resumed continuous motility, in this animal the drug produced prolonged periods of rest alternating with relatively short periods of more or less strong motility.

Figure 3 represents a typical experiment in the human. The drug did not affect normal hunger motility prevailing at the time of injection. After this period of hunger motility had ended, however, the effect of the drug became apparent. The following period of rest was greatly lengthened, and when hunger motility returned, it was of low intensity and atypical for a number of hours.

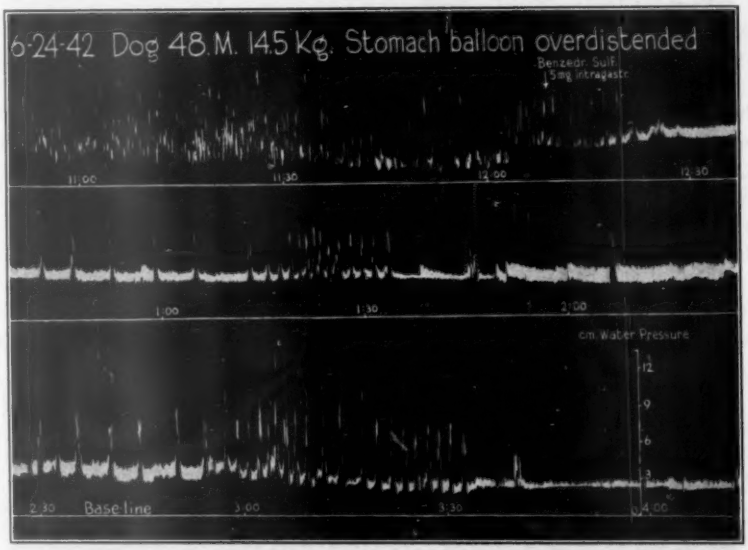

FIG. 2.—Dog unanesthetized, male, 10.6 kg. Continuous gastric motility from overdistention of stomach balloon. At arrow, 5 mg. of amphetamine sulfate in 5 cc. of warm water was administered through a thin catheter, introduced through the gastrostomy cannula. After a latent period of 22 minutes, periods of complete rest alternated with periods of single or repeated contractions; this lasted for about 2 hours, when the test was ended. Time is marked in half-hour periods.

Discussion. Amphetamine is regarded by many clinicians as a sympathomimetic drug, comparable to epinephrine in its biologic effects. This is not quite true, however,[3] and Tainter has called it a pseudo-sympathicotropic drug.[9] Dryness of the mouth is frequently observed in patients following administration of amphetamine. This latter effect is not observed with epinephrine, and may therefore be called atropine-like. It was chiefly this observation that made us feel that amphetamine might affect psychic secretion.

While our experiments in the dog show the absence of appreciable

change in psychic secretion following the drug, this need not be applied to the human. Whenever we are dealing with central nervous effects of drugs, the situation is much more complicated in the human than in any animal. We have not been able to extend the study to young subjects because of technical difficulties.

We cannot explain the variability of the responses of the Pavlov pouch of the same or of different dogs to the injections of amphetamine.

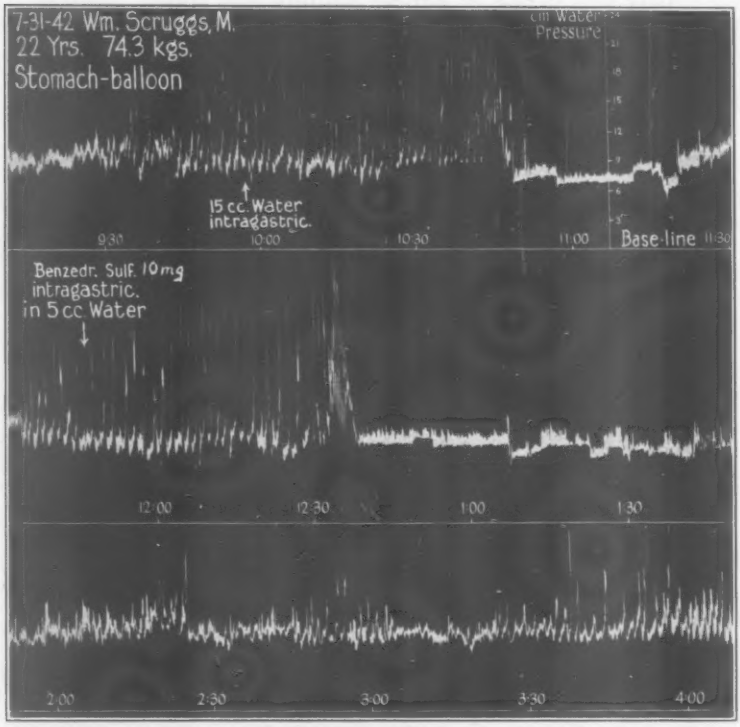

FIG. 3.—Human, 22 years, 74.3 kg. Normal, fasting, stomach balloon. Regular hunger motility. At first arrow, 15 cc. of warm water was injected as control into stomach through the second lumen of the balloon tube. At beginning of second period of hunger motility 10 mg. of amphetamine sulfate in 5 cc. of warm water was injected into stomach (second arrow). After a latent period of 50 minutes motility was more or less absent for 40 minutes and from then on (+2 hours) motility was weak, and no hunger pangs were felt by the subject. Time is marked in half-hour periods.

That is, we do not know why in some animals there is a slight increase, in others a large increase, and in still others no change at all in the secretion and acidity of gastric juice following the injection of histamine and of histamine and amphetamine. The total amount of mg. of HCL secreted was not greater in a number of experiments than in the controls, although it was distinctly greater in the 60-minute samples after injection of histamine and amphetamine.

The suppression of gastric motility in the dog and in the human following the administration of amphetamine either by mouth, intragastric or intraduodenal, or by intravenous injection, was distinct and prolonged in most experiments. Even in those tests in which motility was not abolished completely it was modified. Typical strong hunger contractions were absent but smaller contractions, not sufficient to evoke the feeling of hunger, prevailed. This group of experiments showed conclusively that amphetamine affects the feeling of hunger and probably reduces craving for food. The periods of inhibition appear to be sufficiently long to warrant the assumption that 3 doses of amphetamine per day will probably abolish more or less the feeling of hunger between meals.

We do not assume that the above described effects of amphetamine on hunger motility can explain entirely the reduction in appetite and the loss of weight following the administration of the drug to obese children, but we are inclined to believe, that the psychic effects mentioned before, contribute to a considerable extent.

Summary and Conclusions. The possible causes for the decrease of appetite and the loss of weight of obese children treated with amphetamine sulfate (Benzedrine) were analyzed.

The drug caused increased activity, and mental and physical responses were distinctly increased. The children appeared to be more disciplined under the influence of the drug, and followed their diet with greater ease. These effects were due to the drug rather than to education, "policing" or suggestion during prolonged clinic attendance, because the children regained their appetites and weight when placebos or other drugs were administered.

In laboratory experiments the following results were obtained:

Psychic secretion in the dog was not materially changed by amphetamine sulfate.

The effects of amphetamine on gastric secretion of the dog were inconstant.

Gastric motility in the dog and in the human was depressed considerably following the administration of amphetamine.

It is believed that the psychic effects of amphetamine plus the depression of gastric hunger motility and of hunger can explain the results obtained by us in the treatment of the obese child.

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VACUUM DRIED HUMAN SERUMS IN THE PREVENTION AND TREATMENT OF CERTAIN OF THE COMMON COMMUNICABLE DISEASES—AN 8-YEAR STUDY

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Previous reports[11,12,13,15] have described the clinical use of human serums dried *in vacuo* from the frozen state for the preservation and treatment of certain infectious diseases in relatively small groups of patients. The present report presents the results obtained with such serums over an 8-year period in the prevention of measles, mumps, and chickenpox, and in the prevention and treatment of scarlet fever and whooping cough.

Because febrile and shock type reactions, to be discussed later, occasionally occurred following their intravenous injection in the early years of this work, vacuum dried serums in the present studies were at first used only for intramuscular injection. It now appears that the intravenous injection of vacuum dried serums prepared by the newer techniques is probably as innocuous as the intravenous injection of the same serums prepared in the liquid state.

In view of the fact that these serums may be restored in a small fraction of their original water content, for routine intramuscular use, it has been customary to dissolve the powdered residue from each 10 cc. of serum in 4 cc. of sterile distilled water. This markedly reduces the bulk of the material to be injected; *e. g.*, 20 cc. of serum may be injected as a total fluid volume of 8 cc. For intravenous injection the serum may be restored to its original volume if so desired.

Preservatives have not been added to such serums in the desiccated state, but serum centers operating under license from the National Institute of Health are required to supply with each ampule of desiccated serum an ampule of sterile distilled water containing 0.35% phenol. The purpose of this procedure is to prevent the contamination of such serums following restoration to the fluid state.

Measles Prophylaxis. Both convalescent and normal pooled adult serums have been employed in passive immunization against measles. Particular interest has been paid to the use of vacuum dried normal adult serum in pools containing the bloods of a minimum of 50 individual donors inasmuch as convalescent serum is extremely difficult to obtain in sufficiently large quantities to be of general practical value. Moreover, it is felt that the use of large pools of normal serum

provides a product which varies little from pool to pool whereas small pools or individual bulks of convalescent serum undoubtedly vary tremendously in their protective power. The disadvantage that somewhat larger doses are required when pooled adult serum is employed is offset to a large extent by the advantage that vacuum dried serums are generally concentrated to less than one-half their original volume when restored to the liquid state.

Results comparable to those described here have been reported with the use of liquid pooled adult serum by Gunn,[6] Lempriere,[10] Champlatoup,[3] Bull,[2] and others; the latter two studies were well controlled. Likewise, the results obtained with vacuum dried convalescent serum are quite comparable to those reported in many studies with liquid serum beginning with those of Nicolle and Conseil[14] in 1918.

TABLE 1.—MEASLES PROPHYLAXIS VACUUM DRIED HUMAN SERUM (1233 CASES)

	Convalescent serum 168 cases			Pooled adult serum 1065 cases		
	No disease	Attenuation	Disease	No disease	Attenuation	Disease
Close exposure (desired result often attenuation)	77	40	5	471	273	18
Casual exposure (including hospital)	37	6	3	267	25	11

	Convalescent serum	Pooled adult serum
*Dosage Schedule for Complete Protection:**		
Age 6 years or under	10 cc.†	15–20 cc.
Age over 6 years	15 cc.	20 cc.
Age over 12 years	15–20 cc.	30 cc.

*Dosage Schedule for Attenuation:** Give one-half the dose recommended for complete protection in the first 3 days following the initial exposure. Give two-thirds of the dose recommended for complete protection on the 4th or 5th days following the initial exposure, and the full dose recommended for complete protection on the 6th and 7th days following the initial exposure.

* After the 7th day following exposure, the value of serum is questionable.

† 4–5 cc. diluent used for each 10 cc. of original serum.

The results obtained in measles prophylaxis with both convalescent and pooled normal adult serum are shown in Table 1. The suggested dosage schedule is also given in this table. It will be noted that the cases are divided into a group given serum after close exposure, and a second group whose exposure was casual (including ward exposures). Obviously the expected secondary case rate is much higher following a more intimate exposure.

The results are indicated as "no disease," "attenuation," and "disease." Obviously, the desired result is "attenuation," except in the instance of ward and other institutional exposures where it is important to prevent the spread of an epidemic and in certain very young and delicate children. A case of measles is considered attenuated if fever lasts for no longer than 24 to 48 hours and there are no complications. In general, it is felt that serum administered later than the 7th day following the initial exposure has little effect in modifying or preventing the disease. If either convalescent or pooled adult serum is given in adequate amounts sufficiently early in the incubation period, complete

protection or attenuation will follow in 90% or more of the cases injected.

TABLE 2.—SCARLET FEVER PROPHYLAXIS VACUUM DRIED HUMAN SERUM (1195 CASES)

	Convalescent serum 1043 cases		Pooled adult serum 152 cases	
	No disease	Disease	No disease	Disease
Close exposure	851 (238)	22 (7)	102 (87)	5 (2)
Casual exposure (including hospital)	170 (106)	0	45	0

Figures in parentheses indicate number of cases known to be Dick positive.

*Dosage schedule:**†	Convalescent serum
Age 6 years or under	10–15 cc.‡
Age over 6 years	15 cc.
Age over 12 years	20 cc.

* For pooled adult serum double dose recommended for convalescent serum.
† If exposure continuous repeat serum injection on 10th day.
‡ 4–5 cc. diluent used for each 10 cc. of original serum.

Scarlet Fever Prophylaxis. The value of convalescent scarlet fever serum in passive immunization of exposed individuals is widely recognized. An analysis of many reports, such as that by Hoyne, Levinson, and Thalhimer,[8] indicates that following the injection of liquid convalescent serum, the case incidence in exposed individuals is approximately 2.5%. The results in this study (Table 2) with vacuum dried serum were essentially the same. There was a case incidence of 2.6% in the group receiving convalescent serum following a more intimate exposure, and a case incidence of 2.2% in the group of 1043 cases receiving convalescent serum.

The symptoms in the majority of the 22 cases developing scarlet fever following the injection of convalescent serum were very mild and there were no complications. It is interesting that 8 of these 22 cases developed the disease between the 11th and 20th days following the administration of serum. Furthermore, all 8 cases remained in the same household with the source of contagion. Previously reported studies[12] on the duration of passive immunity following injection of convalescent serum as shown by the Dick test, would suggest that passive immunity lasts on the average from 10 to 14 days. These earlier studies combined with the clinical studies indicate the advisability of repeating serum injections every 10 days when the exposed individual is to remain in the same household with the source of contagion.

When possible an attempt was made to determine the Dick reaction on exposed individuals prior to serum injection. However, in a disease with such a short incubation period as scarlet fever, parents and physicians are often unwilling to lose the 24 hours which is necessary for the performance of the test. As will be noted in Table 2, 351 of the cases here reported were known to have positive Dick tests prior to the injection of convalescent serum.

In order to determine the value of normal pooled adult serum from Dick negative donors, a series of 152 individuals was given this serum following exposure. Eighty-nine of these contacts were known to be

Dick positive. It would appear from the studies reported that in the absence of convalescent serum, pooled adult serum from immune (Dick negative) donors may be effective in preventing the disease.

The dosage schedule employed for both convalescent and pooled adult serums may be seen in Table 2.

Scarlet Fever Treatment. One hundred and sixty-nine cases of scarlet fever have been treated with vacuum dried convalescent serum. A good response was obtained in 129 (76%) of these cases, which is comparable to the results obtained with liquid serum by Hoyne, Levinson, and Thalhimer[8] and others. A good response is characterized by a return to a practically normal temperature, a fading rash and absence of or marked diminution in toxemia within 36 to 48 hours following the administration of serum. From 30 to 60 cc. of serum were given at a dose and in the great majority of cases a single dose of serum was sufficient to secure the desired result. Occasionally 2 and even 3 doses of serum are necessary.

The majority of the cases in the early part of this study were injected by the intramuscular route. It is felt, however, that better results are obtained when serum is administered intravenously, and for several years this has been recommended routinely. More rapid absorption and higher concentration result.

The detailed results may be seen in Table 3.

TABLE 3.—SCARLET FEVER TREATMENT WITH CONVALESCENT SCARLET FEVER SERUM (169 CASES)

Result	No. of patients
Good*	129
Moderate†	24
No response‡	16

Dosage: 30 to 120 cc.
Serum given intravenously gives best results.

* Cases whose symptoms subsided in 36 to 48 hours or less. No complications.

† Cases whose symptoms remained longer but showed definite improvement. No complications.

‡ Cases in which serum had no apparent effect, or in which complications developed.

Prophylaxis and Treatment of Whooping Cough. Previous reports on the use of vacuum dried hyperimmune whooping cough serum have been made by McGuinness, Stokes, and Mudd,[12] McGuinness, Bradford, and Armstrong,[11] and Katsampes, Bradford, and McGuinness.[9] This serum is prepared from the blood of individuals who are known to have had pertussis in childhood and who in addition have received repeated injections of pertussis vaccine. The agglutination titer of such serum varies from 1:1280 to 1:5120 with an average of 1:2560 which is of interest in that the agglutination titer of convalescent serum is usually in the range of 1:300. A report on more recent methods of immunization and titration has been made by Flosdorf, McGuinness, Kimball and Armstrong.[4]

The results obtained in passive immunization following exposure and the dosage schedule employed may be seen in Table 4. When the entire group of 215 cases is considered it will be noted that 168 (78%)

failed to contract the disease, 22 (10.3%) developed very mild whooping cough consisting of a mild cough without whooping or vomiting; 12 (5.6%) developed a mild disease in which there was some whooping but no vomiting; and 13 (6%) developed typical whooping cough which was in no instance followed by complications. Particular significance is attached to the group of 106 infants and young children continuously and intimately exposed to siblings with no attempt at isolation. Among this group 71 (67%) failed to develop any symptoms, 16 (15%) developed very mild pertussis, 8 (7.5%) developed mild pertussis, and 11 (10.5%) typical pertussis.

TABLE 4.—WHOOPING COUGH PROPHYLAXIS HYPERIMMUNE HUMAN SERUM (215 CASES)

	No disease	Very mild disease*	Mild disease†	Typical disease
Intimate exposure (continuous) 106 cases	71 67%	16 15%	8 7.5%	11 10.5%
Intimate exposure (short duration) 60 cases	50 83.4%	6 10%	3 5%	1 1.6%
Casual exposure (includes ward contacts) 49 cases	47 95.8%	0	1 2.1%	1 2.1%
Totals	168 or 78%	22 or 10.3%	12 or 5.6%	13 or 6.1%

* No whooping or vomiting—mild cough of short duration.
† Whooping but no vomiting—short duration.

Dosage of Serum Used:
10–20 cc. depending on age of child and intensity of exposure.‡
A minimum of two 20 cc. injections should be given when exposure continuous.
Serum injection should be repeated in 5 to 7 days.

‡ 4 cc. of diluent used for each 10 cc. of original serum.

The best results appear to be obtained when serum is administered within the first week following the initial exposure.

Vacuum dried hyperimmune serum has been used in the treatment of 315 cases of pertussis following the onset of catarrhal symptoms. Of the 315 cases treated, 123 were infants of 6 months of age and under.

TABLE 5.—WHOOPING COUGH TREATMENT HYPERIMMUNE HUMAN SERUM (315 CASES)

Result	No. of patients	
Excellent	118	= 68.6%
Good	98	
Moderate	62	= 19.7%
Poor	32	= 10.2%
Deaths	5	= 1.5%*
	(3.2% among 123 infants 6 months of age and under)	

Dosage of Serum Used:
20 cc. intramuscularly repeated 3 or 4 times.†
It may be advisable in critically ill infants to give larger doses intravenously.

* Four deaths in infants under 6 months of age, and 1 death in an 18 month infant. None of these 5 infants received a full course (three or more 20 cc. doses) of serum.
† 4 cc. of diluent used for each 10 cc. of original serum.

The results obtained and the suggested dosage schedule may be seen in Table 5. The results are tabulated as excellent, good, moderate,

poor and deaths. An excellent result is one in which virtually all symptoms have disappeared within 1 week of the time serum therapy was instituted. A result is considered good if the major symptoms have disappeared in from 10 to 14 days following the onset of therapy. A moderate result is one in which it can be definitely felt that the symptoms have been lessened by the serum although not in a rapid or spectacular manner.

Four of the 5 deaths which occurred among the 315 treated cases, were in infants 6 months of age or under. Three of these infants were 2 months of age. One died 4 days following the initial dose of serum, having received a total of 40 cc. The second died within 36 hours of the initial dose of serum, having received a total of 40 cc. The third infant died 24 hours after a single 10 cc. dose. All 3 infants were moribund with bronchopneumonia when treatment was first instituted. A fourth infant, age 6 weeks, died 10 days after the initial dose of serum, death being due to an intractable diarrhea. This child likewise received too little serum, having had only two 10-cc. doses, one on the 10th and one on the 5th day prior to death.

One child of 18 months admitted to the hospital in a convulsive state received one 20-cc. dose of serum but died 36 hours after admission.

It appeared necessary to include these cases in this series, although not one had received a full therapeutic course of serum, 3 having died within 36 hours of the initial dose.

In general better results were obtained when treatment was instituted early in the course of the disease. The intravenous administration of 60 to 100 cc. of serum at a dose is now recommended in the case of critically ill infants. It may be desirable to repeat these large doses one or more times.

TABLE 6.—MUMPS PROPHYLAXIS VACUUM DRIED HUMAN SERUM (305 CASES)

	Convalescent serum 200 cases		Pooled adult serum 105 cases	
	No disease	Disease	No disease	Disease
Close exposure	155	18*	38	1
Casual exposure (including hospital)	26	1	60	6†

Dosage Schedule:‡	Convalescent serum	Pooled adult serum
Age under 5 years	10 cc.§	20 cc.
Age 5 to 12 years	15 cc.	20-30 cc.
Age over 12 years	20-30 cc.	30 cc.

* 15 cases developed a very mild disease; 3 cases developed moderately severe mumps.

† 4 cases developed mumps within 5 days after receiving serum.

‡ If serum is given later than 1 week after initial exposure there can be no assurance of protection or modification.

§ 4–5 cc. diluent used for each 10 cc. of original serum.

Mumps Prophylaxis. Vacuum dried serums have been employed in attempted passive immunization of 305 individuals following exposure to mumps. Two hundred cases received convalescent serum, that is serum obtained during the first 4 months following recovery from the disease; and 105 cases received pooled normal adult serum. The

results obtained and the dosage schedule recommended are shown in Table 6.

It is felt that these results are not as accurate as would be desired inasmuch as many of the individuals treated in this series were adults who may have had mumps during childhood and forgotten they had had the disease. However, the series includes a sufficient number of presumably susceptible children who have received serum following close exposure and the data indicate that convalescent serum is probably effective to a certain degree. Its use appears to be justified in the absence of more specific measures. The results presented here are comparable to reports by Hess,[7] Barenberg and Ostroff,[1] and others; but well controlled studies with either vacuum dried or liquid serum have not been carried out.

It is possible that in the absence of convalescent serum, pooled normal adult serum may have some degree of effectiveness in passive immunization against mumps.

TABLE 7.—CHICKENPOX PROPHYLAXIS VACUUM DRIED HUMAN SERUM (239 CASES)

	Convalescent serum 59 cases		Pooled adult serum 180 cases	
	No disease	Disease	No disease	Disease
Home	6	10	23	5
Hospital	42	1	131	21

*Dosage Schedule:**	Convalescent serum	Pooled adult serum
Age under 6 years	10–15 cc.†	20 cc.
Age over 6 years	20 cc.	30 cc.
Age 12 years and over	25–30 cc.	30 cc.

* If serum is given later than 1 week after initial exposure there can be no assurance of protection or modification.

† 4–5 cc. diluent used for each 10 cc. of original serum.

Chickenpox. Vacuum dried convalescent and normal pooled adult serums have been employed in the attempted passive immunization of 239 individuals following exposure to chickenpox. The results obtained and the dosage schedule employed may be seen in Table 7. Passive immunization against chickenpox was relatively unsuccessful. Attempts to prevent the spread of the disease on hospital wards with pooled normal adult serum have, with a few exceptions, failed. A number of the cases of chickenpox developing after the injection of convalescent serum have been mild, but more individuals developed the disease than were protected. These results do not agree with those reported by Gordon and Meader[5] and others who employed liquid convalescent serum. But, as in the case of mumps prophylaxis, well-controlled studies are not yet available for comparison.

On the whole, it would seem that attempted passive immunization against chickenpox with convalescent or pooled normal adult serums is only justified when there are special indications to prevent the development of the disease.

Reactions. In general, reactions following the intramuscular injection of vacuum dried serums are negligible. Local discomfort at the

site of injection generally lasts for from 12 to 24 hours, particularly in older individuals. A few individuals have a slight temperature rise of ½ to 1° F., lasting for 12 to 24 hours. On rare occasions a temperature elevation to 102° F. or 103° F. results. Several cases of delayed serum sickness have been encountered, but the incidence was less than 0.1% of individuals receiving human serum. No acute anaphylactic reactions have occurred following the intramuscular injection of vacuum dried serums.

In the early years of this study a number of sharp febrile and shock-like reactions occurred following the intravenous injection of these serums. It is now felt that these reactions were probably due to early faulty technique in handling the serums prior to vacuum dehydration, for in recent years vaccum dried serums have been given intravenously with no greater occurrence of reactions than with serums prepared and preserved in the liquid state.

Summary. Human serums dried *in vacuo* from the frozen state have been employed in passive immunization against measles, scarlet fever, whooping cough, mumps, and chickenpox, and in the treatment of scarlet fever and whooping cough.

With the exception of chickenpox, in which both convalescent and pooled adult serums frequently failed to protect, satisfactory results have been obtained. The results in mumps prophylaxis are not conclusive, but strongly suggest that serum may be of value.

Particular interest has been focused on the value of pooled normal adult serum in passive immunization against measles, and on the use of "hyperimmune" whooping cough serum in the prevention and treatment of that disease.

It would appear from these studies that serums dried *in vacuo* from the frozen state may be given either intramuscularly or intravenously with no more reaction than from injection of the same materials preserved in the liquid state; and the clinical results are comparable to those reported by other investigators who have employed similar serums preserved in liquid form.

Vacuum dried serums may be stored over long periods of time without deterioration and may be redissolved in a small fraction of their original water content, thus permitting concentration prior to injection.

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TOXIC EFFECTS OF PROMIN (SODIUM P,P′-DIAMINODIPHENYL-SULFONE-N,N′-DIDEXTROSE SULFONATE) ON THE ERYTHROCYTES OF GUINEA PIGS

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In a series of well-controlled experiments Feldman, Hinshaw and Moses[4–6] have shown that promin is an effective therapeutic agent for the control and the cure of experimental tuberculosis in guinea pigs. Promin has also been used successfully to combat infections which were induced by hemolytic streptococci,[19] by pneumonococci[7] or by gonococci.[13]

Following these initial studies on the course of tuberculosis in experimental animals, Hall and his colleagues[10] presented a preliminary report on the data assembled from the blood of patients who had received promin for clinical tuberculosis. These authors confirmed the observation that promin is toxic and showed that the drug caused excessive destruction of the blood, resulting in anemia apparently hemolytic in type.

My interest in these studies on promin evolved from the tentative observation of Feldman that the drug induced anemia in his tuberculous animals. Interested in experimental anemia, I undertook to study the peripheral blood and the hemopoietic organs of normal guinea pigs which were given promin by mouth. Adequate amounts of promin were provided by Dr. E. A. Sharp of Parke, Davis Company and I wish to acknowledge indebtedness to him for his courtesy and interest in this study. This report is restricted to the data assembled from my study of the erythrocytes of these animals.

Methods of Study. Twenty guinea pigs, free from any external evidence of disease and having an average body weight of 317.4 gm., were selected from our stock colony. They were arranged into 4 groups of 5 animals each, housed in metal cages, 2 animals to a cage, and fed our standard ration. One group received 100 mg. of promin daily; a second group, 200 mg. daily; a third group, 300 mg. daily, and a fourth group, water only as controls.

As our study was of short duration, we provided each guinea pig its daily allotment of promin by means of a calibrated pipet inserted into the mouth, instead of adding the drug directly to the diet in a 1% concentration (300 and 400 mg. of promin each day), as in Feldman's study. Promin was given for 21 days in the amounts indicated. It was then withdrawn and the animals were followed for 21 days more, recovery from the toxic effects being observed.

All examinations of blood were made on a single sample withdrawn from the heart with a 2 cc. Luer syringe, equipped with a 23-gauge needle. This

sample was transferred to a chemically clean glass slide and all determinations made from the single sample. The number of erythrocytes per c.mm. was determined in pipets approved by the U. S. Bureau of Standards, using the Bright-Line Improved Neubauer counting chamber. Hematocrit determinations were made with the Van Allen tubes; erythrocyte volumes (in c.μ) from the hematocrit reading and the total erythrocyte count; the amount of hemoglobin (gm. per 100 cc.) by means of the Cenco-Sheard-Sanford photelometer. Two slides were prepared of each sample of blood obtained; one was stained with brilliant cresyl blue counterstained with Wright's stain, for study of the reticulocytes; and the other was stained with the May-Grünwald Giemsa technic.

Results. The daily administration of promin in the amounts stated was apparently without deleterious effect on the general appearance of these guinea pigs during the first week. All increased in weight and their intake of food was satisfactory. During the second week some changes were observed. Loss of appetite and weight was experienced by some animals, so that by the end of the second week 1 animal which had received 200 mg. daily and 2 which had received 300 mg. daily were dead. During the third week the same number of deaths occurred, so that at the end of the third week, when the drug was withdrawn from all animals, there were 14 animals: 5 controls, 5 which had received 100 mg. daily, 3 which had received 200 mg. daily, and 1 which had received 300 mg. daily still alive.

Toxic effects, certainly not evident grossly at the end of the first week, were definitely demonstrated in the samples of blood taken at that time. The effects were most marked in animals which had received the larger amounts of the drug. Cardiac blood was dark in all the experimental animals; but in those receiving 200 and 300 mg. daily, it was thin and of a deep chocolate color. Spectrophotometric examination (by Dr. Charles Sheard) of oxalated samples of blood showed the presence of sulfhemoglobin in some animals and methemoglobin in others. A number of blood samples included an intermediate, as yet undetermined, product which had an absorption band of 626 to 628 m.μ. These pigments were not in the plasma, but in the erythrocytes, for centrifuged samples contained a clear supernatant plasma, but dark, almost black, packed erythrocytes. These pigments are the result of some chemical changes in the hemoglobin induced by promin after its passage through the gastro-intestinal mucosa; for we have not seen such color changes as yet when the drug was given intravenously.

TABLE 1.—ERYTHROCYTE DATA ASSEMBLED AFTER 1 WEEK OF ADMINISTRATION OF PROMIN

(The figures in parentheses indicate ranges observed)

Amount of drug daily mg.	No. of animals	Erythrocytes, mil. per c.mm.	Volume of erythrocyte, cubic microns	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes
None	5	5.41 ± 0.08 (5.20 – 5.95)	82.7 ± 1.1 (80.0 – 87.0)	12.7 ± 0.3 (11.2 – 13.6)	1.2 ± 0.2 (0.6 – 2.5)
100	5	4.40 ± 0.06 (4.05 – 4.60)	88.6 ± 1.4 (84.4 – 96.5)	10.5 ± 0.3 (9.1 – 11.2)	7.8 ± 0.6 (4.8 – 11.2)
200	5	3.56 ± 0.20 (2.90 – 4.45)	116.5 ± 3.2 (98.9 – 130.0)	10.5 ± 0.5 (8.8 – 12.0)	5.2 ± 0.9 (2.3 – 8.9)
300	5	3.54 ± 0.20 (3.05 – 4.35)	111.1 ± 3.9 (92.0 – 125.7)	9.3 ± 0.2 (8.5 – 9.8)	11.8 ± 2.3 (3.0 – 24.0)

All data on the toxic effect of promin on the erythrocytes assembled at the end of the first week were condensed into Table 1. Average determinations, together with their standard errors, are given, and the range or spread of the data is also included. Data assembled from the 5 control animals were not altered significantly from those obtained from the 20, prior to giving promin (Table 2). But animals which had received 100 mg. of the drug each day now showed a significant decline of their total erythrocyte counts and of concentration of hemoglobin, together with an increase of cell volumes and of reticulocyte percentages.

TABLE 2.—CONTROL DATA BEFORE ADMINISTRATION OF PROMIN

No. of animals	Sex	Body wt., gm.	Erythrocytes, mil. per c.mm.	Volume of erythrocyte, cubic microns	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes
20	M	317.4 (280–352)	5.40 ± 0.07 (4.75 – 6.10)	82.1 ± 1.8 (75.4 – 90.5)	13.0 ± 0.09 (11.6 – 14.6)	1.8 ± 0.2 (0.7 – 3.9)

All animals did not respond alike to comparable amounts of promin. Of the 5 which received 200 mg. daily, 1 at the end of the first week had an erythrocyte count of 2,900,000 in each c.mm. of blood, while a mate had a count of 4,450,000, which was close to the lower limit of the normal range. Regenerative capacities, indicated by cell volumes and reticulocyte percentages, were most marked in animals which had sustained the greatest toxic damage.

Whereas the distribution induced in animals by the daily doses of 200 mg. was significantly different from that of those given 100 mg., there were no essential differences between the data derived from the 200 mg. and 300 mg. groups. The addition of 100 more mg. did not appear to inflict any more damage on the red cells than did 200 mg. of drug. The degree of anemia, the extent of the macrocytosis and the hemoglobin levels were statistically alike in the 2 groups at the end of the first week. There was, however, a significant difference in their reticulocyte percentages. This is due to the fact that 1 animal, which had an erythrocyte level of 3,000,000 in each c.mm., had the unusually high reticulocyte level of 24%.

At the end of the second week the degree of anemia was greater than before in animals which had received the daily doses of 100 mg. The mean number of erythrocytes had dropped to 4,080,000, and their size had increased to a mean of 105.7 c.μ. Hemoglobin levels and reticulocyte percentages remained unchanged. But in both groups which received the larger amounts of the drug, increased toxic changes, greater than those recorded at the end of the first week, were not observed at the conclusion of either the second week or the third week of administration of promin. The animals appeared to acquire a tolerance for the drug and manifested a blood regenerative capacity which maintained the levels of erythrocytes and hemoglobin at a satisfactory minimum. Elevated percentages of reticulocytes were proof that the bone marrow had not been injured seriously by the drug.

In Figures 1, 2, 3 and 4, stained smears show the appearance of the erythrocytes in the blood of a normal animal and of animals at the end of the third week of administration of promin. Reticulocytosis,

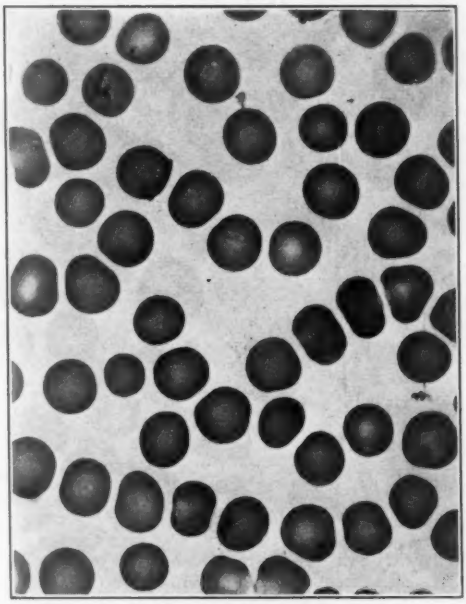

FIG. 1.—Blood smear of a normal guinea pig.

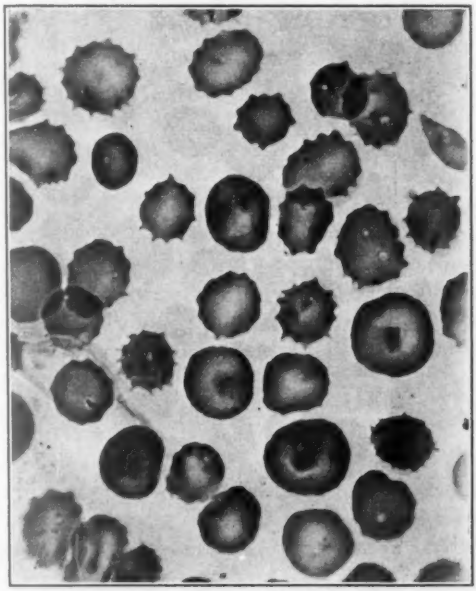

FIG. 2.—Blood smear of guinea pig after receiving 100 mg. of promin daily for 3 weeks. Polychromatophilia, regeneration and crenation are shown.

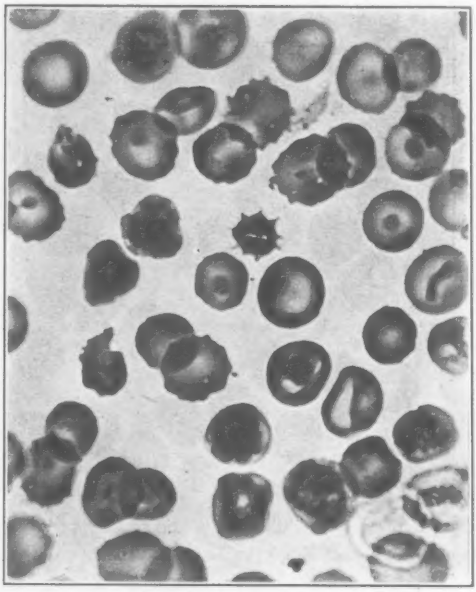

FIG. 3.—Blood smear of guinea pig after receiving 100 mg. of promin daily for 3 weeks. Reticulocytes are shown, but they are not crenated.

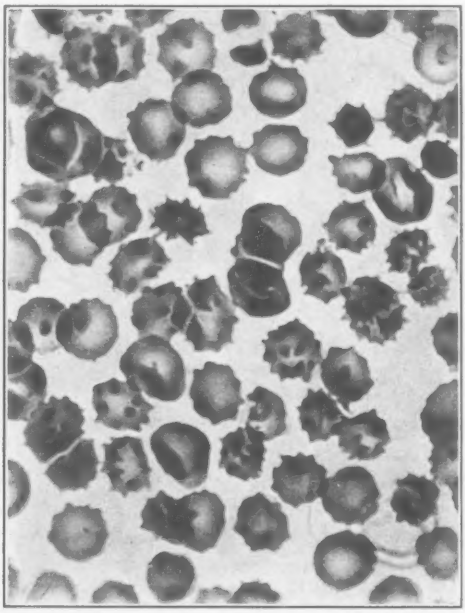

FIG. 4.—Blood smear of guinea pig after receiving 200 mg. of promin daily for 3 weeks. Most of the erythrocytes in the circulating blood are crenated.

macrocytosis, hyperchromatophilia and crenation of the mature erythrocytes have occurred.

To determine the irreversibility of these changes induced in the erythrocytes by promin, we withdrew the drug from all animals but continued to observe the blood at weekly intervals for 3 weeks thereafter. Elevated erythrocyte counts, reduced erythrocyte volumes and increased hemoglobin levels occurred immediately. The data, assembled after the third week of recovery, from the 14 surviving animals is presented in Table 3, showing that promin had not induced any permanent damage to the hemopoietic system.

TABLE 3.—DATA ASSEMBLED 3 WEEKS AFTER DISCONTINUING ADMINISTRATION OF PROMIN

Amount of drug daily mg.	No. of animals	Erythrocytes, mil. per c.mm.	Volume of erythrocyte, cubic microns	Hemoglobin, gm. per 100 cc.	Reticulocytes, % of total erythrocytes
None	5	5.77 ± 0.15 (5.35 – 6.76)	81.7 ± 2.05 (70.0 – 88.0)	13.9 ± 0.31 (13.2 – 15.3)	1.14 ± 0.15 (0.6 – 2.0)
100	5	4.87 ± 0.12 (4.30 – 5.48)	91.8 ± 2.88 (80.3 – 106.9)	12.7 ± 0.22 (12.4 – 13.0)	1.7 ± 0.28 (0.8 – 3.1)
200	3	4.55 ± 0.12 (4.20 – 4.95)	99.8 ± 3.56 (90.9 – 111.1)	12.3 ± 0.47 (11.2 – 13.0)	1.2 ± 0.29 (0.5 – 2.3)
300	1	4.90	95.9	12.4	1.4

Comment. Changes which were induced in the blood of the guinea pigs by promin resembled qualitatively those hitherto described following the administration of sulfanilamide, other sulfonamides[14–18] and drugs.[1,2,9,11] They conform in general to those which occurred following the administration of the drug to tuberculous patients. Feldman, Hinshaw and Moses[6] gave 300 to 400 mg. daily in their diets to guinea pigs weighing 500 gm. Therefore their doses ranged from 600 to 800 mg. daily per kilogram of animal weight. The average weight of our guinea pigs was 317.4 gm., so that our doses ranged from 310 mg. per kilogram of body weight in the group which received 100 mg. daily to 930 mg. per kilogram of body weight in the group which received 300 mg. daily.

The effect of the drug is apparently directly on the erythrocyte and the anemia which ensued is the result of chemical and physical changes in the erythrocytes (Fig. 4), their destruction, and their final removal from the blood stream, largely by the spleen. Accompanying these changes, pigments were formed in the cells, so that samples of blood drawn a week after administration of promin was started were very dark and showed by spectrophotometric analysis the presence of sulfhemoglobin, methemoglobin and in certain animals an additional product as yet undetermined, but having its own characteristic absorption band.

Crenation of erythrocytes, observed in "cover slip" preparations of the blood of animals given promin, will occur equally well in *in vitro* preparations. When varying concentrations of promin were added to oxalated preparations of whole blood, crenation occurred immediately, and in fresh "cover slip" preparations the proportion of such crenated cells was found to correlate with the amount of promin added to a given sample of blood. Crenated cells, however, were not identified

in "cover slip" preparations made of heart blood taken from an animal which had received the drug by way of the saphenous vein. It is likely that following an intravenous injection the protective organs, liver, spleen and bone marrow, readily remove all damaged cells from the circulation. But the slow absorption from the gastro-intestinal tract of the orally administered drug resulted in a continuous action so that damaged erythrocytes were encountered more readily. These changes are somewhat like those hitherto described, when erythrocytes are subjected to other substances which set up changes of permeability and osmotic pressure, and perhaps in the cell membrane itself.[3,9]

The blood picture in these animals is, in some respects, like that of clinical hemolytic anemia.[8] Typical spherocytosis of the erythrocytes, such as found in familial hemolytic (spherocytic) anemia, however, was not observed in these bloods. Other symptoms of hemolytic anemia, such as increased pigment content of the bile and of the urine, elevated percentages of reticulocytes and greatly enlarged spleens, were observed in these animals.

In clinical hemolytic anemia, erythrocytes begin to hemolyze at higher concentrations of solutions of sodium chloride than do normal erythrocytes. In other words, they are more fragile and less resistant to hypotonic solutions. In normal guinea pigs, Musser and Krumbhaar[16] showed that hemolysis began at 0.42% of sodium chloride and was complete at 0.31% of sodium chloride. More recently Kato[12] stated that hemolysis began at 0.45% and was complete at 0.33%. Our data show the range to be from 0.44% to 0.30%. Blood samples, taken from animals which had had promin daily for 2 weeks, showed an increased resistance in that beginning hemolysis occurred at 0.40% sodium chloride concentration, and complete hemolysis at 0.20% concentration.

Summary and Conclusions. A study of the effects of promin (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate), when given orally to guinea pigs, on erythrocytes is reported. Five guinea pigs were given 100 mg. daily; five, 200 mg.; five, 300 mg.; and five served as controls. The following conclusions were drawn from the study:

1. Promin is a toxic drug and in large amounts may kill an animal. At the end of 3 weeks of daily administration, 2 animals were dead in the group which received 200 mg. daily, and 4 were dead in the group which received 300 mg. daily.

2. Promin exerts a direct toxic effect on the erythrocytes, manifested by the presence of abnormal hemoglobin pigments in the cells and by changes in the surface membranes, so that in fresh "cover slip" preparations many cells are crenated.

3. Damaged erythrocytes are removed from the blood stream by the spleen. Anemia is induced, the spleens are greatly enlarged and percentages of reticulocytes are elevated.

4. The anemia is a hemolytic anemia, although some of the features of familial hemolytic (spherocytic anemia) were not present. The erythrocyte volume was increased, spherocytosis was absent, and resistance to hypotonic salt solution was increased.

5. The blood and the spleens were excessively dark. Spectrophotometric analysis showed the presence in the erythrocytes of sulfhemoglobin, methemoglobin and an additional unidentified pigment which had an absorption band intermediate between those of sulfhemoglobin and methemoglobin.

6. Promin did not induce any permanent damage of the bone marrow. Regeneration of erythrocytes, indicated by reticulocytosis, macrocytosis and polychromatophilia, proceeded in the face of continuous administration of large amounts of the drug.

7. Morphologic changes, induced in erythrocytes *in vivo* by promin, may be observed in *in vitro* preparations as well.

8. Although the drug is toxic, no permanent damage to any part of the organism was observed when sublethal doses were given.

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FEBRILE REACTIONS RESULTING FROM THE READMINISTRATION OF SULFADIAZINE*

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It has become an accepted fact that unfavorable reactions occur less frequently in patients treated with sulfadiazine than in patients to

* These studies were undertaken when both authors were members of the staff of the Pennsylvania Hospital.

whom sulfanilamide, sulfapyridine or sulfathiazole has been given.[1,12,18] It has also been established, however, that the use of sulfadiazine is not without danger, and that undesirable reactions may result from its use.[1,3,6,7,8,11,12,13,14,19,20,24] Several investigators have reported acquired sensitivity to the sulfonamide drugs.[4,10,12,17,21,22,23,24,25] The term "acquired sensitivity," as used here, is intended to imply a sensitivity resulting from either (*a*) prolonged continuous administration of one of the sulfonamide drugs, or (*b*) readministration of the same drug after an interval of time has elapsed. Lyons and Balberor[15] state that the administration of a second course of sulfathiazole resulted in a febrile reaction in 36% of their cases, whereas in those patients who received the drug in one continuous course which lasted for 7 or more days, the incidence of fever was 10.4%. They also state that no febrile reaction was seen in patients prior to the 9th day after the initial exposure to the drug.

The observation of several patients who exhibited unfavorable reactions to sulfadiazine led us to make the following survey. In order that our data on sulfadiazine might be compared with the published data on sulfathiazole, we have in most respects followed the methods of Lyons and Balberor.[15]

TABLE 1.—CONDITIONS FOR WHICH SULFADIAZINE WAS ADMINISTERED THERAPEUTICALLY

Condition	No. of patients
Lobar pneumonia	7
Empyema thoracis	1
Bronchopneumonia	1
Lung abscess	2
Pneumonia due to *B. aërogenes*	1
Virus pneumonia	1
Ischiorectal abscess	1
Cystitis	1
Stab wound of chest	1
Infected index finger	1
Ulcerative colitis	1
Superficial infection of abdominal wound	1
Chronic infection involving chest wall	1
Total	20

Material. Thirty-seven patients who had received one course of sulfadiazine were given a second course. Of these, 20 had received the first course for therapeutic purposes (Table 1), and 17 patients were given a first course of sulfadiazine for experimental purposes. The reasons for hospitalization of the latter group are listed in Table 2.

Dosages. The dose of sulfadiazine used therapeutically in the group of 20 patients varied in the initial amount from 2 to 4 gm., followed by 1 gm. every 4 to 6 hours throughout the first course. Each patient in the experimental group received an initial dose of 4 gm., followed by 1 gm. every 4 hours for 6 doses, then by 1 gm. every 6 hours for 8 doses, or a total of 18 gm. The amount of the drug used in the second course was the same for all patients as the first course given to the experimental group, except in those cases exhibiting a reaction.

The mean duration of the first course in all patients was 6.97 days, with a variation of from 2 to 30 days. The second course was started in from 8 to 50 days (mean time 15.4 days) after the completion of the first course. No patient in the series had shown evidence of fever for at least 5 days prior to the commencement of the second course.

TABLE 2.—CONDITIONS AFFECTING THOSE PATIENTS WHO RECEIVED SULFADIAZINE FOR EXPERIMENTAL PURPOSES

Condition	No. of patients
Syphilitic heart disease	2
Myocardial infarction	2
Arteriosclerotic heart disease	1
Hypertensive heart disease	1
Cerebral hemorrhage	1
"Saturday night palsy"	1
Dermatomyositis	1
Minimal pulmonary tuberculosis	4
Gastric ulcer	1
Gastric hyperacidity	1
Eczema	1
Diagnosis not established	1
Total	17

TABLE 3.—PATIENTS WHO REACTED TO THE SECOND COURSE OF SULFADIAZINE

Case	Reason for 1st course	Duration 1st course (days)	Interval between courses (days)	Max. temp. (° F.)	Chill	Rash	Psychosis	Total white count during reaction	Remarks
H. G.	Cystitis	10	12	100.4	+++	+	+++	10,600	Toxic psychosis for 12 hrs.
R. S.	Virus pneumonia	8	16	100.0	0	0	++	Not done	Severe delirium for 3 to 4 hrs.
L. A.	Experimental	3	28	100.0	Sl.	0	0	Not done	Slight malaise
L. C.	Infected finger	10	11	99.8	0	++	0	Not done	Reacted to: 1st course,
				102.0	0	+	0	4,900	2d course of 2 gm.,
				100.0	0	0	0	Not done	3d course of 0.25 gm.,
N. S.	Ischiorectal abscess	18	20	102.8	+++	+++	+++	5,850	Delirium for 4 to 6 hrs.,
				101.4	++	+	++	6,000	reacted to: 1st course,
				101.2	+	0	+		2d course of 2 gm., 3d course of 1 gm.
R. L.	Ulcerative colitis	10	17	100.0	0	+	0	9,000	Delirium for 4 to 6 hrs.
				101.0	0	0	0	Not done	reacted to: 1st course, 2d course, did not react to 2 gm. of sulfanilamide or sulfapyridine

Studies. Blood sulfadiazine levels were determined on the 2d or 3d days of both courses in most patients, and were consistently between 6 and 14 mg. per 100 cc. If the duration of the treatment was longer than 4 days the determination was often repeated. Blood counts (hemoglobin and total white count) were taken on every patient before and after each course, and a differential count was done in most cases that showed a reaction of any type. The differential distribution was never altered from the normal, and the total white counts were not remarkable, as may be seen in Table 3. The urine of every patient was examined at regular intervals, and nothing untoward was discovered in routine studies (*i. e.*, no red cells, casts or albumin). Crystals of sulfadiazine were not infrequently seen in the urine specimens, but no attempt was made to correlate their presence or absence with the occurrence of a febrile reaction.

Criterion for Reaction to the Drug. Our arbitrary criterion for a significant reaction to sulfadiazine was a fever of at least 100° F. which could not be explained on the basis of any other mechanism.

The most frequent manifestations of a reaction were, in addition to fever, chills or a sensation of chilliness, diffuse skin eruptions, severe malaise, and toxic psychoses. These signs and symptoms all appeared, as a rule, within a few hours after the onset of the second course, and always appeared within 24 hours of that time. The administration of the drug was stopped as soon as fever became manifest or when any other evidence heralded a reaction.

Results. Of 37 patients who were given a second course of sulfadiazine, 6 (16.2%) had fever during the second course, 3 (8.1%) reacted to both the first and second courses, and 3 (8.1%) reacted to only the second course. Four had a diffuse maculopapular eruption, and all had either frank chills or chilly sensations.

A third course was given to 2 of the patients (L. C. and N. S., Table 3) who had reacted to the second course. The reaction was reproduced with each course.

One patient (R. L., Table 3) who reacted to the first course had received sulfathiazole immediately prior to the sulfadiazine, and he reacted to the latter on the 9th day of its administration. He subsequently failed to react to sulfapyridine, or sulfanilamide, but did respond again to sulfadiazine. Another patient (N. S.) had fever, rash, and delirium 3 days after the cessation of the first course, 21 days after its beginning. He subsequently reacted to a second and third course. Four patients (R. L., R. S., N. S. and H. G.) had delirium which was far out of proportion to the amount of fever.

Once a reaction had occurred the fever persisted for periods which varied from 12 to 48 hours.

Comment. It is well known that toxic reactions to the sulfonamides are most likely to occur in those cases to whom the drug has been administered continuously for periods of 9 or more days, or to whom the drug is readministered after an interval of several days.[12]

In order to determine with the greatest significance the effects of readministration, one would wish to know the incidence of reactions in the aggregate of the patients who received the drug for at least 9 or more days. The incidence of fever in response to sulfadiazine therapy is reported as 3%;[5,13] 1%;[12] as apparently very rare;[10] 1.6%;[6] 0.2%;[8] and 0.5%;[9] or an average of about 1.5%. One may assume that most of these cases received the drug for less than 1 week, and can only reiterate the statement that the less prolonged courses are less likely to yield reactions.

In our series, 10 cases received a first course of sulfadiazine which was 10 or more days in length, and 3 (30%) had a reaction to the first course. The mean length of the first course in these patients was 14.2 days, with extremes of 10 and 30 days. Two of the 3 patients who reacted to only the second course had received a first course which was longer than 8 days. These facts are admittedly not of sufficient scope for significant statistical analysis, although they prompt the suggestion that febrile reactions are more likely to occur in patients receiving prolonged courses of sulfadiazine than is at present appreciated.

Lyons and Balberor noted a much higher incidence of febrile reac-

tions to the readministration of sulfathiazole than to the administration of the first course. They attributed this increase to the development of hypersensitivity to the drug during the interval. The same thing is true, but to a lesser degree, in our series of sulfadiazine readministration, particularly among those patients who received the drug initially for short periods. We do not feel that there is sufficient evidence, however, that the development of sensitization is enhanced by an interval between courses in contrast to the continuous prolonged administration of the sulfadiazine. We have nothing new to add to the theories of the mechanism of the reactions to sulfonamides which have been discussed in recent publications.[2,16,25]

This study indicates that reactions to sulfadiazine are less severe than those reported for sulfathiazole. One feature of the reactions to sulfadiazine which was of particular interest was the occurrence of severe delirium in 4 cases. It usually lasted only a few hours but was out of all proportion to the amount of fever present. We cannot be certain that these febrile reactions are, in themselves, productive of permanent injury. Nevertheless, it is clear that until evidence is presented which shows definitely that they are not harmful, this drug, as well as other sulfonamide compounds, should be used with increasing discretion and caution.

Summary. 1. Six of 37 patients (16.2%) experienced a febrile reaction to sulfadiazine. Three (8.1%) experienced a febrile reaction to both the first and second courses and 3 (8.1%) to the second course.

2. Febrile reactions to a second administration of sulfadiazine are less frequent and less severe than those reported for sulfathiazole.

3. Febrile reactions to the readministration of sulfadiazine are frequently accompanied by delirium, chill, and a maculopapular rash.

4. Sulfadiazine, as well as the other commonly used sulfonamides, should be given only in those cases which with certainty justify its administration, although no evidence is presented to show that the febrile response *per se* is harmful.

We wish to express our thanks to Miss Harriett Hosmer, R.N., for her willing and careful assistance with this work; and to Dr. L. S. Carey, Dr. John B. Flick and Dr. Walter E. Lee, for their permission to study patients who were on their services at the Pennsylvania Hospital.

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STUDIES ON 2-SULFANILAMIDO-4-METHYL-PYRIMIDINE (SULFAMERAZINE, SULFAMETHYLDIAZINE) IN MAN*

II. TOXIC MANIFESTATIONS

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IN a recent paper[3] we reviewed the experimental data pertaining to the therapeutic activity, pharmacologic behavior, and toxicity of sulfamerazine (2-sulfanilamido-4-methyl-pyrimidine, sulfamethyldiazine), and presented observations on the absorption, distribution, and excretion of the drug in man. The purpose of this communication is to discuss certain toxic effects which have been encountered following the clinical use of sulfamerazine† in the treatment of several types of infection.

Clinical Material and Methods. Included in this study are the first 200 unselected patients‡ who were treated with sulfamerazine for at least 4 days, or received no less than 10 gm. of the drug. For the most part they included adult patients suffering with acute infection, such as pneumococcal pneumonia, the bacterial meningitides, gonococcal urethritis, and non-specific urinary tract infections. In general, the drug was given orally, with an initial dose of 3 gm., followed by 1 gm. every 6 to 8 hours until the temperature had remained normal for 48 to 72 hours. In severe infections, such as meningitis, the initial

* This work was aided by a grant from the Sharp & Dohme Laboratories, Glenolden, Pa.

† Sharp & Dohme Laboratories, Glenolden, Pa., kindly supplied the sulfamerazine used in this study.

‡ These cases were treated at the Hospitals of the University of Pennsylvania and the Philadelphia General Hospital and will be included in future reports dealing with the therapeutic effectiveness of sulfamerazine.

dose of 3 gm. was usually administered by vein (sulfamerazine sodium) and followed by 1 gm. by mouth every 4 hours. Patients with urinary tract infections received 2 gm. of the drug daily at 12 hour intervals in equally divided doses. The range of dosage in the entire series was from 10 to 114 gm., given over periods varying from 4 to 24 days. With the exception of 10 cases of gonococcal urethritis, all of the patients were hospitalized and were closely followed with appropriate laboratory studies. Fluids were given liberally, usually from 2000 to 3000 cc. a day, but none of the patients received alkalies.

Toxic Manifestations. A summary of the various toxic manifestations encountered in 200 patients receiving sulfamerazine is given in Table 1. Toxic reactions, attributable to the drug, excluding simple crystalluria, were noted in 30 patients (15%).

TABLE 1.—SUMMARY OF TOXIC MANIFESTATIONS OCCURRING DURING TREATMENT WITH SULFAMERAZINE (200 CASES)

Toxic effect	No. of cases	%
Hematuria:*		
Microscopic	16	10.0
Gross	2 (1)†	1.3
Acute loin pain	1	0.5
Nausea and vomiting	8 (1)†	4.0
Rash	6	3.0
Fever	5	2.5
Leukopenia	4 (1)†	2.0
Thrombocytopenia	1†	0.5
Psychosis	2	1.0

* On the basis of 160 cases (40 urologic patients were excluded).
† Massive dosage (Table 3).

Urinary Tract Complications. Clinical experience with the sulfonamides, excepting sulfanilamide, has shown that the toxic effects involving the urinary tract, namely hematuria, suppression of urinary output and renal colic, represent the most significant untoward manifestations. These complications are related to solubility of the drugs, especially the acetyl derivatives. Because of the relatively greater solubility of both sulfamerazine and acetylsulfamerazine in urine,[4] as compared to the sulfonamides now in common use, one might expect to encounter less urinary tract toxicity with this compound. In this series of cases crystalluria was observed in 36 patients (18%); but we have not considered the presence of crystalluria as evidence of urinary tract involvement unless it was associated with other urinary complications. No doubt additional cases of crystalluria would have been detected if every specimen of urine voided during each 24 hour period had been examined.

Microscopic hematuria, as evidenced by the finding of red blood cells in a single specimen, was encountered in 10% of the patients. Although we have attributed this urinary abnormality to sulfamerazine, it should be stressed that in many instances the patient's disease might well explain these findings when one considers the type of infections under treatment. Four of the cases in this sub-group showed occasional crystals of the drug in the urine.

Gross hematuria was observed in 2 patients; and in 1 of these acute loin pain was also present. Because of the importance of these un-

toward reactions, a few remarks concerning the salient features of both cases are worthy of special comment.

Case Studies. Case 1 (Table 2). A. W., a white woman, aged 18, was treated in a routine manner with sulfamerazine for meningococcal meningitis. The patient responded well to chemotherapy and her illness was uneventful until the 14th day of treatment, at which time she suddenly experienced a sharp pain in the right loin region. Following this attack, which lasted approximately 20 minutes, the patient was catheterized and a sample of urine from the bladder contained many crystals of the drug and innumerable red blood cells. At no time after the attack did the patient offer any symptoms or laboratory evidence of any urinary tract disturbance. As indicated, the urinary output was 1300 cc., or better, for the 24 hour periods preceding, the day of, and following the apparent ureteral blockage. The serum drug levels, taken several hours before the attack, were not excessive and, although the degree of acetylation was higher than is usually seen with sulfamerazine,[3] it was in keeping with previous readings in this case. A total of 77 gm. of the drug had been given before the onset of the urinary toxic reaction, after which the drug was discontinued.

Table 2.—Acute Loin Pain and Gross Hematuria

Case 1. A. W., a white woman, aged 18. Type I meningococcic meningitis with bacteremia successfully treated with sulfamerazine

Day	Dose (gm.)	Serum sulfamerazine			Fluid intake (cc.)	Urine					Blood				Comments
		Free (mg./100 cc.)	Total (mg./100 cc.)	Acetylated (%)		Output (cc.)	Specific gravity	Reaction	Crystals	R.B.C.	Hemoglobin (%)	Leukocytes per c.mm.	Neutrophils per c.mm.	Urea nitrogen (mg./100 cc.)	
1	3*	..	..	..	1500	900+	1.027	Acid	0	0	92	15,500	12,400	..	Vomiting on admission
2	6*	10.8	13.7	21	3550	?	..	..	..	..	..	..	..	32	Vomiting
3	6*	10.5	13.4	22	1930	600+	..	..	0	0	81	..			
4	6	10.0	16.2	38	1400	?	..	..	..	..	77	15,100	13,000		
5	6	8.5	14.3	40	2300	?	..	..	0	0	81	..	..	21	
6	6	6.5	10.7	39	2945	?									
7	6	5.2	6.7	22	2265	?	1.030	Acid	0	0	79				
8	6	6.4	8.2	22	2840	?	..	..	..	..	79				
9	6	7.3	9.1	19	1760	450+	1.020	Acid	0	0	63				
10	6	7.4	9.4	21	2220	800+	..	..	..	..	84	9,800			
11	6	9.6	14.0	32	2310	1350+	..	..	..	..	76	8,000			
12	6	8.5	12.5	32	2800	800+									
13	6	12.0	15.8	24	2600	1300+	1.020	Acid	+	0					
14	2	9.9	13.4	36	3500	1350+	..	..	++++	Gross					Acute loin pain
15	..	1.9	..	..	3750	1850+	1.020	Acid	+	0	70	6,800	..	6	Symptom-free
16	..	0.1	..	..	3000	1400+	1.015	Acid	0	0	..	..	..	6	
17	..	..	..	..	2550	1350+									
18	..	..	..	..	..	..	..	..	..	..	70	6,200	..	8	

* Intravenous administration (5% sulfamerazine sodium).

Case 2 (Table 3). R. S., a white male, aged 30, was given a massive dose of sulfamerazine for subacute bacterial endocarditis. During the first 3 days of chemotherapy the patient received a total of 14 gm. of the drug with no apparent untoward effect. On the morning of the 4th day he was given 25 gm. (sulfamerazine sodium) by vein over a 30 minute period. A free drug level taken 1 hour after the infusion was 106 mg. per 100 cc. of serum. The first

Table 3.—Gross Hematuria and Hypoplasia of Bone Marrow

Case 2. R. S., a white male, aged 30. Subacute bacterial endocarditis unsuccessfully treated with massive sulfamerazine therapy

TABLE 3.—GROSS HEMATURIA AND HYPOPLASIA OF BONE MARROW

CASE 2. R. S., a white male, aged 30. Subacute bacterial endocarditis unsuccessfully treated with massive sulfamerazine therapy

		Sulfamerazine								Urine					Blood					
		Serum			Urine															
Day	Dose (gm.)	Free (mg./100 cc.)	Total (mg./100 cc.)	Acetylated (%)	Free (mg./100 cc.)	Total (mg./100 cc.)	Acetylated (%)	Daily excretion (gm.)	Fluid intake (cc.)	Output (cc.)	Specific Gravity	Reaction	Crystals	R.B.C.	Hemoglobin (%)	Leukocytes per c.mm.	Neutrophils per c.mm.	Platelets per c.mm.	Urea nitrogen (mg./100 cc.)	Comments
1	2	..	..	..	..	..	..	..	..	..	1.017	Acid	0	0	58	6300	4300			
2	6	..	..	..	..	..	..	..	..	..	..	..	0	0						
3	6	22.8	24.6	7.3	..	..	..	..	..	..	..	..	..	+	..	..	..	..	12	
4	25*	106.0†	113.4†	6.5	..	..	..	..	2500	550	..	..	0	0	..	7000	..	..	..	Blood transfusion 500 cc.
5	0	79.4	85.2	6.7	439.0	606.3	27.5	2.42	4525	400	1.026	Alk.	++++	Gross	70	7100	..	..	7	Vomiting
6	0	44.9	49.2	8.8	459.0	770.3	40.3	13.09	4000	1700	1.014	Acid	++	++	53	6800	5000	..	7	Vomiting
7	0	19.7	21.3	7.4	357.5	516.3	30.7	4.12	4000	800	..	Acid	++	+	57	6000	..	..	6	Vomiting
8	0	10.0	11.0	9.9	131.0	207.5	36.9	4.14	3710	1960	..	..	0	0	58	3500	..	..	6	
9	0	4.4	4.4	..	26.3	49.4	26.5	1.97	2240	4430	..	..	..	..	55	7500				
10	6	2.0	2.0	..	13.1	23.5	44.2	0.55	3120	2350	..	..	..	..	62	8800				
11	8	..	..	..	..	..	..	..	3010	700										
12	5	..	..	..	..	..	..	..	2220	850	1.022	Alk.	++	0	56	4000				
13	..	26.1	27.6	5.4	..	..	..	..	2360	850+										
14	..	..	..	..	..	..	..	..	3130	?	1.023	Acid	0	0						
15	..	..	..	..	..	..	..	..	3130	1450	1.019	Alk.	0	0	49	4000				
16	..	..	..	..	..	..	..	..	2200	700	..	..	0	0	45	1700	816	..	10	Blood transfusion 500 cc.
17	..	..	..	..	..	..	..	..	3200	750+	..	..	0	0	52	1500	840			
18	..	..	..	..	..	..	..	..	2800	1650	1.015	Acid	0	0	54	1150	230	..	..	Blood transfusion 500 cc.
19	..	..	..	..	..	..	..	..	..	..	..	..	..	Occ.	57	1400	250	..	..	Blood transfusion 500 cc.
20	..	..	..	..	..	..	..	..	..	..	..	..	..	10–20	54	1800				
21	..	..	..	..	..	..	..	..	..	..	1.015	Alk.	..	Occ.	64	2200	440	..	..	Blood transfusion 500 cc.
22	..	..	..	..	..	..	..	..	..	..	1.017	Alk.	0	Occ.	70					
23	..	..	..	..	..	..	..	..	..	..	..	..	..	..	74	2400	480	..	..	Hypoplastic bone marrow
25	..	..	..	..	..	..	..	..	..	..	..	..	..	..	82	2400	..	18,000		
26	..	..	..	..	..	..	..	..	..	..	1.022	Acid	0	0						
27	..	..	..	..	..	..	..	..	..	..	1.022	Alk.	0	0	80	6500				
29	..	..	..	..	..	..	..	..	..	..	..	..	..	..	78	6800	4600	20,000‡		

* Intravenous administration (5% sulfamerazine sodium).
† One hour after infusion.
‡ Normal platelet count 1 week later.
Days 24 and 28 are omitted as they offered no significant data.

voided specimen of urine following the massive dose of sulfamerizine showed many crystals of the drug and innumerable red blood cells. For the next 48 hours the urine sediment continued to show microscopic crystalluria and hematuria. This patient probably suffered a partial suppression of urinary output, in that, although his urinary output was never less than 800 cc., the diuresis to be expected from his large intake did not occur until the 5th day following his acute episode, when he excreted 4430 cc. of urine. As indicated, the patient was again given sulfamerazine by mouth with no further urinary disturbances.

In a further attempt to detect any harmful effect of sulfamerizine on the kidney, sections of the kidneys from 5 patients who had died of their disease (including the above patient, R. S.), were examined; no renal damage was found which could be attributed to the drug.

Nausea and Vomiting. Eight patients (4%) experienced some degree of nausea and vomiting during the administration of sulfamerazine. Of these, 6 were cases of meningitis and, although the drug was continued, the vomiting gradually subsided. These cases are included in spite of the fact that the vomiting was probably due to the meningitis. The 7th represented a patient suffering with subacute bacterial endocarditis who had previously received sulfadiazine with severe nausea and vomiting and, following 12 gm. of sulfamerazine, it was also necessary to stop the drug because of this toxic effect. The other instance of vomiting occurred in a man with subacute bacterial endocarditis who was given massive sulfamerazine therapy (Table 3).

Dermatitis. Skin rashes, attributable to sulfamerazine, were encountered in 6 (3%) patients. The rash was scarlatiniform in 1 case and morbilliform or maculopapular in the others. In 1 of the patients the rash appeared on the 20th day, after 113 gm. of the drug had been given. Sulfamerazine was stopped and the rash rapidly disappeared, only to reappear when the drug was again started, and at this time it was accompanied by an elevation in temperature of 105° F. The patient subsequently was given sulfadiazine and developed a rash after 2 weeks' medication. In the other cases the rash appeared on the 4th, 5th, 9th and 10th days of treatment.

Fever. Although it is often difficult to determine whether an elevation in temperature above normal is due to the drug or the infection, we have made the diagnosis of drug fever in 5 (2.5%) patients. The fever in these cases was encountered on the 7th, 8th, 10th, 14th, and 40th day of sulfamerazine therapy, respectively. In 2 of the patients the expected fall in temperature was somewhat slower following the withdrawal of the drug than one usually sees in cases with drug fever.

Blood Disturbances. Four patients developed leukopenia (less than 4000 leukocytes per c.mm.) on the 6th, 8th, 9th, and 12th day of sulfamerazine therapy. In 3 the total white blood count soon returned to within normal limits after the withdrawal of the drug. The fourth patient (Table 3) had, in addition to this finding, thrombocytopenia and a fall of neutrophils to 250 per c.mm. A biopsy revealed a generalized hypoplasia of the bone marrow. Within 2 weeks, following repeated

blood transfusions, the peripheral blood picture returned to normal. There were no cases of acute hemolytic anemia or agranulocytosis.

Nervous and Mental Manifestations. In view of past clinical experience with the sulfonamides containing a methyl group[2] (sulfamethylthiazole, sulfanilyl dimethyl-sulfanilamide), one could presume that sulfamerazine might possibly give rise to certain neuropathologic changes. Welch and his associates,[4] working with several species of experimental animals, have given particular attention to this matter. It was found that dogs or monkeys, given large doses of sulfamerazine over 30 day periods, showed no evidence of nerve injury; but chickens with high blood concentrations of the drug developed definite nerve lesions, although the changes were no greater than those resulting from lower blood levels of sulfadiazine in the same species.

No case of peripheral neuritis was observed in this study. Two patients presented mental symptoms while receiving sulfamerazine, which were possibly due to the drug. The first, a moderately ill pneumonia patient, became disoriented and quite violent on the 3d day of treatment. The mental symptoms subsided promptly after the drug was stopped. The second patient, a chronic alcoholic, confused on admission, became progressively worse mentally during the time sulfamerazine was given, but, because of the seriousness of his illness, chemotherapy was continued for 5 days and the mental changes cleared while the drug was being administered. Not included in Table 1 is a young girl who was given 15 gm. of sulfamerazine sodium intravenously and following this injection experienced generalized twitchings of the body, simulating an attack of tetany. This phenomenon was interpreted as probably due to a "tubing" reaction, but may have been the result of sulfamerazine intoxication.

Summary and Conclusions. 1. Sulfamerazine was given to 200 unselected patients suffering with acute bacterial infections.

2. Toxic reactions possibly due to the drug appeared in 30 instances (15%), though in many of these instances it was not possible to determine whether they were due to the disease or to the drug itself.

3. Gross hematuria was observed in a single case receiving routine sulfamerazine treatment and 1 additional case receiving massive intravenous therapy.

4. No case of peripheral neuritis was seen, although 2 patients developed transient mental symptoms following sulfamerazine therapy.

5. On the basis of this short series, it appears that sulfamerazine is probably no more toxic than the sulfonamides now in common use[1] and that further clinical trial is justified.

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THE RELATIONSHIP BETWEEN RIBOFLAVIN INTAKE AND THIAMIN EXCRETION IN MAN*

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In the course of a recent study of the metabolism and storage of members of the vitamin B complex in patients subjected to surgical procedures, it became necessary to determine their urinary excretion of riboflavin and thiamin. These determinations early suggested that the administration of thiamin alone was followed in some instances by an increased urinary excretion of riboflavin. Therefore, it appeared of interest to investigate this phenomenon further and to determine whether or not the administration of large amounts of thiamin to human beings over a long period of time eventually would induce clinical evidence of riboflavin deficiency. The results of that study form the subject of the present report.

Methods. *Thiamin.* The yeast fermentation method of Schultz, Atkin and Frey[6] was used. Determinations were made on aliquots of 1, 3, 24, or 72-hour specimens which had been acidified with glacial acetic acid and kept at 10° C. or less in a dark ice chest.

Riboflavin. The determinations were done by the technique of Ferrebee.[1] The urines were collected in the same manner as were those for the determination of thiamin. In certain instances, the microbiologic method of Snell and Strong[7] was used to check the values obtained by the fluorescence technique of Ferrebee.[1]

Tests of Body Saturation of Thiamin and of Riboflavin. The methods used to ascertain thiamin and riboflavin saturation in the body were those of Holt and Najjar.[4,5] Both these tests measure the portion of administered vitamin retained by the body under controlled conditions.

Diets. All short time experiments (in which measurements were carried out over a period of a few hours) were done in fasting subjects. The subjects who were studied over a period of several days took 2 types of diets: (*a*) Those individuals who were not hospitalized continued to eat a normal diet with the following exceptions—no synthetic vitamins, medications, alcohol, beer, or glandular meats. Their meat and milk intake from day to day was relatively constant. (*b*) The remaining subjects who were hospitalized were given a diet in which the protein, carbohydrate, and fat intakes were constant. Intake of medications, alcohol, vitamins and glandular meats likewise was restricted.

Clinical Material. The clinical material consisted of the following groups: *A.* Three hospitalized patients were used in the thiamin tolerance experiments.[4] One had melanoma with extensive metastases; the second had uterine fibroids; and the third, carcinoma of the rectum.

B. The effect of large amounts of thiamin given daily for from 2 to 67 days was ascertained on 13 individuals. Of these, 8 were normal, and the remainder

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were hospitalized patients who presented the following disorders: 1, dysmenorrhea of unknown cause; 1, atrophic gastritis; 2, hepatic cirrhosis; and 1, Paget's disease of bone.

Of this group, 6 of the 8 normal individuals were later given larger amounts of thiamin, and for a longer period of time, in an attempt to induce in them a riboflavin deficiency.

C. The last group consisted of 4 individuals who received several injections of thiamin over a period of 4 hours only. One individual was normal, the second had carcinoma of the breast with extensive metastases, the third lymphatic leukemia, and the fourth had melanoma with distal metastases.

Results. *A. Experiments to Test the Effects of the Administration of Thiamin on the Excretion of Riboflavin over a Period of 4 Hours.* The thiamin tolerance test of Holt and Najjar[4] was carried out in 3 individuals. This test was repeated in 2. The content both of thiamin and of riboflavin was determined in each urine specimen. These measurements indicated that, in all instances, the injection of thiamin alone was followed by an increased excretion of both thiamin and riboflavin. Moreover, the increased excretion of riboflavin was independent of the urine volume (Table 1).

TABLE 1.—THE URINARY EXCRETION OF RIBOFLAVIN AFTER THE INJECTION OF 1 MG. OF THIAMIN

			0–½ hr.		½–1 hr.		1–2 hrs.		2–3 hrs.	
	Fasting output*		After thiamin administration							
Subject	Mg./ml.	Mg./hr.	Mg./ml.	Mg./½ hr.	Mg./ml.	Mg./½ hr.	Mg./ml.	Mg./hr.	Mg./ml.	Mg./hr.
E. T.	0.13	13	0.48	36	0.09	5	0.03	6	0.11	12.0
	0.16	15	0.37	34	0.30	8	0.07	11	0.10	14.0
R. B.	0.12	9	0.34	21	0.18	7	0.06	12	0.05	19.0
	0.20	8	0.28	12	0.37	9	0.16	10	0.05	14.0
F. S.	0.33	15	0.63	15	0.46	7	0.50	9	0.50	7.5

* 15 hours after the last meal.

Since the "riboflavin" excreted was measured by a fluorescence method,[1] it was possible that the parenteral administration of thiamin was followed by an increased excretion of material which had the fluorescent property of riboflavin, but nevertheless was not that vitamin. It was necessary, therefore, to demonstrate that this fluorescent material actually was riboflavin, and not some degradation product of thiamin. The fluorescent properties of thiamin itself are very much different from those of riboflavin.[3] To date, the only metabolic product of thiamin known to appear in the urine is a pyrimidine compound which has the ability to accelerate yeast fermentation.[2,11]

Accordingly, large amounts of this pyrimidine accelerator of yeast fermentation (2-methyl-5-methoxyethyl-6-aminopyrimidine) were added to urine samples whose "riboflavin" fluorescence was known; this addition did not effect the amount of fluorescence observed.

There still remained the possibility, however, that the parenteral administration of thiamin resulted in the excretion of another but unknown fluorescent metabolite of thiamin or of a material not related to that vitamin and also not related to riboflavin. For this reason, measurements of riboflavin in urine specimens of individuals who received thiamin were made both by the fluorescence technique of Ferrebee[1] and by the microbiologic method of Snell and Strong.[7] The

results of all determinations were in good agreement. It was evident, therefore, that the administration of thiamin to these subjects was followed by an increased excretion of a substance which had at least two properties of riboflavin: its fluorescent characteristics and its ability to accelerate the growth of *Lactobacilli casei* (Table 2).

TABLE 2.—EFFECT ON THE EXCRETION OF RIBOFLAVIN AFTER THE ADMINISTRATION OF 1 MG. OF THIAMIN TO SUBJECT F. S. COMPARISON OF RESULTS OBTAINED BY DIFFERENT METHODS

	Determination by	
	Fluorescence technique, mg./ml.	Microbiologic technique, mg./ml.
Fasting level	0.33	0.25
0–½ hr.	0.63	0.63
½–1 hr.	0.46	0.45
1–2 hrs.	0.50	0.45

B. Experiments to Test the Effect of the Daily Administration of Thiamin on the Excretion of Riboflavin. Since an increased excretion of riboflavin followed the injection of as little as 1 mg. of thiamin, it seemed possible that the urinary excretion of riboflavin after the daily administration of large amounts of thiamin might induce a serious loss of riboflavin. To test this possibility, 13 subjects were studied. The excretion of riboflavin in the urine of these individuals was measured each day during a control period of from 3 to 7 days. At the end of these periods, each individual was given thiamin chloride in amounts from 10 to 80 mg. per day and measurements of the excretion of riboflavin were continued. An increased riboflavin output was considered significant when: 1, an increased concentration as well as an increased total amount was excreted; 2, the increase was at least 40% above the average control value; and 3, the increase persisted for more than one 24-hour period.

The results obtained in these individuals were less consistent than were those of the short experiments previously described. Four of the 13 subjects took a constant diet, while the others were allowed to continue their routine work and diet under the conditions previously described. Of the 13 subjects given thiamin, 8 excreted temporarily increased amounts of riboflavin. The remaining 5 did not excrete significantly increased amounts; 4 of these were normal individuals and the fifth was a patient with cirrhosis of the liver.

The results obtained indicate that the maximum increase in total excretion of riboflavin in those 8 instances in which an increase was observed, varied from 40% to 560% and the average increase of this group was 225%. The increase in the concentration of riboflavin varied from 43% to 520%, and the average was 180%. No individual maintained the increased excretion for more than 8 days despite continued administration of thiamin.

An increased amount of thiamin was given to 3 normal subjects after the first period of increased riboflavin excretion was over. In all, a second but smaller increased excretion of riboflavin followed the augmented thiamin administration. In 2, a further increase in the

amount of thiamin was followed by a third period of increased excretion of riboflavin. On the other hand, in 2 other subjects in whom no initial increased excretion of riboflavin had been noted after the first administration of thiamin, no increased excretion could be induced by giving even larger amounts of thiamin. Many of the determinations of riboflavin in the urines of this group of subjects were made both by the fluorescent method of Ferrebee[1] and by the microbiologic method of Snell and Strong.[7] The values obtained by both methods checked well (Table 4).

TABLE 3.—EFFECT OF THE DAILY ADMINISTRATION OF THIAMIN ON THE EXCRETION OF RIBOFLAVIN

Subject	Duration of control period, days	Average daily riboflavin excretion during control period		Amount of thiamin administered parenterally		Maximum excretion of riboflavin after thiamin		Duration of increased excretion, days	% increase in excretion of riboflavin after administration of thiamin	
		Mg./ml.	Mg./24 hrs.	Average daily dose, mg.	Duration of administration, days	Mg./ml.	Mg./24 hrs.		Concentration	Total excretion per day
A. T.	3	0.18	400	10	3	0.35	1100	3	95	170
M. Z.	3	0.35	480	40	2	0.50	900	2	43	88
E. H.	4	0.25	400	30	2	0.50	1600	3	100	300
N. N.	6	1.00	1200	30	53	2.30	2900	7	130	140
M. P.	6	0.34	320	35	67	0.42	450	0	23	40
G. F.	6	1.30	1200	40	7	1.50	1300	0	15	8
J. J.	5	0.75	900	20	10	0.70	1200	0	0	33
R. H.	5	0.40	600	50	41	2.50	4000	7	520	560
R. M.	4	0.32	900	30	2	0.37	900	0	16	0
F. B.	4	0.47	375	50	17	0.72	560	7	52	49
H. F.	8	0.19	340	80	13	0.25	480	1	31	41
M. H.	5	0.18	210	50	67	0.75	800	8	320	270
E. B.	3	0.18	550	20*	7	0.35	900	7	190	160

* By mouth.

TABLE 4.—COMPARISON OF VALUES OBTAINED BY DIFFERENT METHODS DURING THE PERIOD IN INCREASED EXCRETION OF RIBOFLAVIN AFTER THE ADMINISTRATION OF THIAMIN

Subject	Determination by	
	Fluorescence technique, mg./ml.	Microbiologic technique, mg./ml.
1	0.76	0.72
2	0.68	0.65
3	0.68	0.66

C. Experiments to Test the Possibility that the Daily Administration of Large Amounts of Thiamin Might Deplete the Body Stores of Riboflavin. Since the administration of thiamin was followed by an increased excretion of riboflavin in 8 of 13 subjects studied, it seemed possible that continued administration of thiamin eventually might deplete the body stores of riboflavin and produce clinical evidence of a deficiency of that vitamin. This deficiency might be manifest also by a continued decrease in the amount of riboflavin excreted, and by an abnormal retention of riboflavin when that vitamin was administered (the riboflavin tolerance test of Holt and Najjar[5]).

To study this possibility, 6 normal individuals were given parenterally from 30 to 60 mg. of thiamin chloride per day for from 11 to 73 days. At the end of these studies none of the subjects had developed clinical signs of riboflavin deficiency. Only 1 excreted less riboflavin than he did during periods before the administration of thiamin. The other 5 subjects excreted amounts of riboflavin similar to those during

the control period. None of the 6 showed any increased retention of riboflavin as determined by the riboflavin tolerance test (Table 5).

D. Experiments to Test the Effect on the Excretion of Riboflavin of Multiple Small Doses of Thiamin Over a Short Period of Time. It has been shown in a previous section of this communication that an increased output of riboflavin followed within a few hours the injection of 1 mg. of thiamin to fasting subjects. On the other hand, when thiamin was administered daily over a period of several days, no sustained, increased riboflavin excretion followed. Hence, it appeared desirable to ascertain the effect on the excretion of riboflavin of multiple 1 mg. doses of thiamin given at intervals of from 30 to 60 minutes.

TABLE 5.—EFFECT OF THE DAILY ADMINISTRATION OF THIAMIN OVER A PROLONGED PERIOD OF TIME ON THE EXCRETION OF RIBOFLAVIN IN THE URINE

Subject	Duration of control period, days	Average excretion of riboflavin during control period		Amount of thiamin administered parenterally		Average excretion of riboflavin at end of experiment		% retention of test dose of riboflavin at end of experiment
		Mg./ml.	Mg./24 hrs.	Average daily dose, mg.	Duration of administration, days	Mg./ml.	Mg./24 hrs.	
N. N.	6	1.00	1200	30	68	0.80	1200	58
M. P.	6	0.34	320	35	73	0.34	312	50
R. H.	5	0.40	600	50	42	0.70	970	40
M. H.	5	0.18	210	50	72	0.13	180	64
F. B.	4	0.35	540	60	18	0.28	470	46
H. F.	8	0.23	408	60	11	0.15	220	48

Measurements of riboflavin excretion were made in the urine specimens collected each hour from 4 individuals who received 1 mg. of thiamin every 30 or 60 minutes for from 4 to 5 doses. In 2 of the 4 subjects an increased excretion of riboflavin occurred. In one this increase persisted for only 2 hours, whereas in the other the increased riboflavin output was maintained for the duration of the experiment.

This increased excretion of riboflavin in 2 of the 4 subjects compares well with the incidence in which the phenomena was noted in the 13 individuals given thiamin over long periods of time.

Discussion. From the data presented it would appear that in certain persons a relationship exists between the thiamin intake and riboflavin excretion. The existence of a relationship between these 2 vitamins already has been demonstrated in experimental animals. The transient mobilization of riboflavin from the tissues into the liver of thiamin deficient rats has been found to be considerably impaired, but that metabolic defect can be corrected when adequate thiamin supplements are administered.[8]

It is possible, therefore, that the administration of large amounts of thiamin to the subjects included in the present study might have initiated a similar transfer of riboflavin from the tissues into the liver, and in the course of that shift a portion of the compound was spilled into the urine. Evidently, the magnitude of this loss was not great enough to produce any clinical evidence of riboflavin deficiency nor could a deficiency of that vitamin be detected by the tolerance test used in this investigation.[5]

Recent studies have demonstrated[10] that rats whose diets were free of all members of the vitamin B complex except for small amounts of

riboflavin (2 μg. per day) gained weight at a slower rate and had a higher incidence of mortality when large supplements of thiamin were fed. However, these effects of thiamin were not noted when the riboflavin supplement was increased to 10 μg. per day.

Clinical evidence of interrelationship between members of the vitamin B complex have been noted by others. Sydenstricker called attention to the fact that the administration of single B vitamins will stimulate the appearance of lesions commonly associated with a deficiency state of other members of the B complex.[9] However, it would appear from the present study that a deficiency of riboflavin could not be induced readily in individuals who probably were not deficient in vitamins B by the long continued administration of thiamin.

Summary. 1. The administration of thiamin to human beings in many instances is followed by transitory increased excretion of riboflavin in the urine. No explanation for the relationship is at hand.

2. It has not been possible to induce either clinical or chemical evidence of riboflavin deficiency in these individuals by the daily administration of large amounts of thiamin for as long as 73 days.

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PROGRESS
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PEDIATRICS

UNDER THE CHARGE OF
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THE CHILD IN WAR

By Irving J. Wolman, M.D.

Every environmental change has its reflection on the child living within that environment. There is hardly a child on the face of the globe whose life is not being altered in some way by the current war. To a greater or less degree each must contend with shortages of food and other necessities, infectious agents on the move, abnormal emotional experiences, altered home conditions and family relationships, and all kinds of deviations from a peaceful normal pattern of living. The modern pediatrician cannot escape becoming concerned over the expected harmful effects of this war upon the children now enduring its hardships, and so quite naturally he turns back to the records of the last great war to discover what general trends and principles were noted by the child specialists of $2\frac{1}{2}$ decades ago.

The medical papers published during World War I and afterwards fail to reconstruct the full picture of the War's effects upon the European child. Scientific studies on health and growth are surprisingly limited in numbers, and most seem incomplete and inadequate when judged by current standards of scholarship. For example, there are many references to such disorders of malnutrition as rickets, but the diagnostic criteria and the presentation of control statistics are as a rule not published. And few of the studies contain the complete body of data or even a representative fraction, so that the reader may judge for himself the validity of the author's conclusions. Of course, inside of combat zones and occupied territory the military exigencies may block all opportunities for the collection of good scientific records, and statistics on mortality and morbidity in populations churned up by war are subject to suspicion as to completeness and reliability. Even in less violently disturbed areas most doctors are too occupied with more pressing and urgent tasks to note down in quantitative terms the full mass of their observations. Furthermore at the time of the last war much of the present understanding of vitamins and nutritional requirements was perhaps dreamed of but otherwise absent, and the fundamental standards by which we try to evaluate growth and nutrition were still in the nursery stage of development. Together with these limitations of the pediatric history of World War I, no medical scholar has attempted an exhaustive detailed

compilation and interpretation of original source material. The closest approach to this ideal treatise are some of the chapters in the monographs on public health during the war sponsored by the Carnegie Endowment for International Peace. The volumes from Germany[11] and from Austria Hungary[42] are richer in pertinent information than those from France[4] and Italy;[39] but unfortunately the contributing authorities have as a rule neglected to annotate their generalizations and impressions with references or footnotes.

For the present review, the aim has been, not to compile any sort of comprehensive compendium, critical or uncritical, but rather to summarize briefly a few of the more objective and scientific reported contributions. The effort was made to restrict the selected papers to those dealing with child health and growth. The topics of nutrition, feeding and epidemiology, about which much can be found, are merely touched upon. The latter part of this review describes a few important reports from the present war. One cannot but hope that those medical workers in the child health field on the other side of the water will continue to collect and record significant observations with equal assiduity and under circumstances as similar as possible to those of the pre-war period, so that later on it will be possible to draw comparisons between the contemporary child's wartime status and that of peacetime years.

The Effect of Malnutrition Upon Intelligence and Behavior. One of the best studies made in this field was that of Blanton,[5] who studied the entire school population of a German city near the war zone. While stationed at Trier (population 55,000) with the American Army of Occupation, he made a psychiatric survey of some 6500 school children, ranging from $5\frac{1}{2}$ to 14 years of age. The food blockade had not yet been lifted and hunger and malnutrition were still widespread. In March 1915 the German Government had taken control of the nation's grain supply, and by 1916 every variety of food except green vegetables was being rationed. The bread, which was everybody's food, became progressively more coarse, and by 1918 the rye and other flours were present in essentially unmilled form. Rubner[46] showed that this inferior bread not only causes intestinal disturbances but yields to the digestive tract of the adult but 60% of its protein and 85% of its calories. With young children the loss by failure of absorption was even greater. Bruns and Hartman[9,10] reviewed the meals of 2413 school children in Trier and found that only 68 were receiving milk. A child's official diet for 1 day was as follows:

Breakfast: 95% unmilled rye bread, marmalade of turnips and beet molasses.
10 A.M.: Bread, marmalade.
NOON: Potatoes, war soup containing little or no fat, perhaps bread.
4 P.M.: Bread, marmalade.
6 P.M.: Potatoes, soup, bread.

On Sundays sausage or herring and butter or margarine were added. Nearly every family supplemented this starvation ration with food purchased from illegal sources; but the poor could not afford enough extra items to procure anything near an adequate diet. It was found that approximately half of the children had been on starvation rations for 2 to 3 years. During the winter of 1918–19, the American observers encountered an appreciable amount of sickness among the children, the most common infections in the order of frequency being influenza, pneumonia, tuberculosis and middle ear disease. Comprehension of lessons was found poor and slow, their attitude disinterested and their wits dull. It was

believed that the fatigue and restlessness were caused not alone by malnutrition but by actual hunger as well, since many of the children came to school from homes lacking food for breakfast. In striking contrast the youngsters from more prosperous households were bright, strong and active, and seemed to do well in their classes. To be sure there had been environmental factors other than the chronic food shortage to disturb children. Thousands of troops and many wounded had been kept in the city, often being quartered temporarily in the school houses. Most of the male teachers had been called to military service. Many fathers were away at the front, and home discipline was consequently relaxed. Numerous air raids and the even more frequent air alarms were continually interrupting the children's activities both in school and at home. But the most important single factor in retarding their educational progress seemed to be the poor nutrition and physical starvation of the children themselves.

Effects of War Upon Children's Mental Condition. Can malnutrition cause feeblemindedness? To answer this question Blanton examined every retarded and dull child to be found in the school system, using as criteria low school grades and the results of a modified intelligence quotient test. Marked mental retardation regarded as due to malnutrition alone was found in 135 (2.08%), and malnutrition plus infection found in an additional 2.57%. Another group (2.74%) was judged as being scholars of borderline ability who under favorable circumstances could manage to keep abreast of the class by dint of hard work, but when handicapped by lack of sufficient food could not keep up, even though the pace of teaching was appreciably slower. Thus about 8% of all the children showed signs of serious injury to the nervous system due to starvation. Blanton made a thorough search of the school population for evidences of psychologic and psychiatric disorders. Among the 6500 children there were but 15 truants, 25 extremely nervous and emotionally unstable, 6 epileptics, 1 dementia precox, 5 with organic lesions and only 2 with true neuroses, both being highstrung timid girls reacting in this fashion to the deaths of their fathers on the battlefield. The percentage of major nervous and mental disturbances which could be attributed to the war was therefore small indeed. Many children however did display nervous symptoms of mild degree. They were afraid to go to sleep; dreamed with terror about bombings; tossed restlessly all night. Some worried constantly over relatives killed or captured; many would cry whenever war or their fathers were mentioned. No instances of incoherent stuttering or stammering were present, but the majority of children in the first and second grades suffered from mild speech defects such as slurring and lisping, indicating that the fine coördinations essential for good speech were being interfered with. This behavior was more conspicuous among the underweight and ill-fed youngsters.

Thus more than 90% of the children endured the 3 year starvation period without suffering any major emotional disorder or permanent deterioration of mental capacity. The minor disturbances, though common, were expected to clear up as the restrictions on food became eliminated and life returned to a more peaceful level. Many parents told Blanton that their children's slight terrors and nervousness began to fade away soon after the Armistice was signed.

Effects of War Upon Infant Health. During the first 2 years of the war, no change in weight or length of newborn German babies was observed in spite of the fact that many mothers were showing evidences of faulty nutrition as a consequence of the beginning food shortage.[29] But from the

third war year on, the birth weights of newborns regularly fell a little, being some 50 to 100 gm. below the peacetime level. The figures from Oppelm showed the mean weight of newborns in 1917 and 1918 to be below 3000 gm.[29] Recovery from the physiologic loss of weight in the neonatal period was slowed somewhat, and the frequency of stillbirths, prematurity and congenital debility of the newborn increased a little. But it was the general impression among obstetricians as stated by Sellheim[29] that even when a mother undergoes great physical strain and privation during the entire pregnancy the fetus would show few evident signs of injury and that the baby as a rule would appear in good condition when born.

In blockaded countries the infants and children suffered great malnutrition as a consequence of the lack of cow's milk and other important nutrient foods. Infantile diarrhea and other digestive disorders, scurvy, rickets, skin diseases, intestinal parasites, influenza, the acute exanthems, tuberculosis, and every sort of contagion and nutritional disturbance crowded the out-patient clinics and hospitals in tragic reflection of the mass starvation and dearth of essential supplies. For summaries of these and related epidemiologic problems in the European countries the reader is referred to the above-mentioned publications of the Carnegie Endowment for International Peace. A good introduction to the problems of feeding the hungry people both during and after the Great War will be found in the same series of monographs, in publications from relief organizations such as the American Red Cross[2,31,33,52] and the American Food Relief Administration,[55] and in the paper of Mason.[36]

Infant mortality statistics from countries actively engaged in the war at close range showed an increase during the war period and until shipments of food were sent in after the blockade was lifted. Data from some of the warring countries are shown in Table 1:

TABLE 1.—DEATH RATES FOR INFANTS 1 YEAR AND UNDER (PER 1000 LIVE BIRTHS)

	France[4]	Austria[21]	Budapest[7]	Italy[28]
1911	153.8	201.4	161.5	
1912	105.0	166.6	138.3	135.1
1913	110.2	179.9	146.2	
1914	109.1	169.3	154.9	127.3
1915	113.0	**210.7**	174.3	142.4
1916	112.1	**198.3**	152.8	146.2
1917	**131.4**	**188.2**	**185.4**	142.6
1918	**151.1**	**191.5**	**178.0**	**181.5**
1919	124.9	157.1	156.4	
1920	123.7	159.2	181.0	
1921–23	98.5	...	...	123.6

The data in Table 1 were reported from nations at war, some for a time being invaded or occupied. No correction has been made for the abnormally low birth rates which were observed from 1914 through 1919.[18] For this as well as other considerations inherent in the sources of the data, the columns should not be compared one with another, but only viewed vertically. Bókay and Juba,[7] who presented the Budapest figures, comment that the supply of cow's milk and other baby foods was so scanty there that had it not been for mother's milk many more babies would not have survived; they observed that the percentage of infants being raised on breast milk had gone up significantly in comparison with the previous years of peace.

For many years the children born under the trying conditions of the

hunger blockade were looked upon by the local physicians as a handicapped group, unusually susceptible to illness and slow to convalesce.[29]

Glands of Internal Secretion. Curiously, after the war had been over for several years there came reports from scattered areas in Germany of goiters developing in school girls and adolescents. Lill[32] reported from Wurzburg, a community with normally a low goiter rate, that the incidence of thyroid enlargement had risen in the years 1922 through 1925 from a usual rate of 1.1% to 2.8% up to between 3% to 11% in the various age groups of the school girls. In Mannheim, where goiter once had been uncommon, Stephani[51] found that, in 1924–25, 35% of the boys and 37% of the girls had visibly enlarged thyroids, often tumor-like. No explanation was apparent to the observers for this disturbance of thyroid function.

Rickets, especially the late variety in children over 5 years of age, became common in the clinics of Germany and Austria in the late war and post-war years.[16,26,29] For example, Engel[16] in Berlin encountered some 63 cases of late rickets in 1916, 26 in 1917, 62 in 1918 and 141 during 1919. Undoubtedly faulty food and hygiene played major rôles in the causation of this osteomalacic disturbance, but perhaps additive factors of hormone character were active also.

Starvation may retard the onset of menstruation, according to Calmette[12] and Heuyer.[25] The conclusion was based on studies of the French children of Lille who had experienced 4½ years of semi-starvation during the German occupation. When surveyed after the Armistice all were said to show retardation of weight, height and chest circumference, though measurements were not published. Tuberculosis was found to be much more prevalent than before the war, judged by chest findings and enlarged cervical nodes. During the occupation, scurvy, peripheral neuritis and pellagra had been common,[30] and several outbreaks of dysentery had occurred. Calmette's examination showed that but 20 of 100 girls at the age of 18 had as yet established a regular menstrual rhythm, and Heuyer found 8 out of 12 of that age who were not yet regular. Heuyer stated also that signs of hypothyroidism were frequent.

Tuberculosis. An increased incidence of childhood tuberculosis was reported from all parts of Germany[38] and Austria Hungary.[42] Thus in Stettin[29] the tuberculosis death rate for children which from 1910 to 1915 had ranged between 0.35 to 0.40 per 1000, had tripled to 1.2 in 1916–17, 0.94 in 1917–18. Equally striking are the data on the increased frequency of positive reactors to the Pirquet skin tuberculin test from Berlin,[15] Charlottenburg,[56] Vienna,[48] Rostock[28] and Munich.[3] Among children in institutions and of the low income group in various cities during the war, the positive reactors ranged from 20% to 30% at the early age of 2 years —taking the figures for this age as an illustration—whereas prior to 1914 the incidence in the same communities was between 9% to 12%. Bartschmid's[3] values for Munich were as follows:

TABLE 2.—TUBERCULOSIS INCIDENCE IN MUNICH

Age of children (in years)	Percentage of positive reactors	
	1912-1914	1915-1919
1	12.8	13.9
2	19.6	24.8
3–4	25.8	44.1
5–6	32.7	51.7
7–8	47.6	54.2
9–10	43.6	**63.3**
11–12	50.0	56.6
13–14	**64.9**	57.4

Schick and Wagner[48] record the appearance of great numbers of children with severe scrofula and malignant forms of pulmonary consolidation in the University pediatric clinic of Vienna in the years after the war. Langstein and Rott[29] found that where poverty was greatest, food, clothing and fuel most inadequate and sanitary facilities very rudimentary or absent, that there the spread of tuberculosis among the children was found most rampant. They noted that the years of financial depression and currency inflation which followed the war were even worse than those of the war itself. All observers agreed that the fundamental factors responsible for the enhanced spread of childhood tuberculosis were diminished bodily resistance consequent to malnutrition and poor hygiene of living plus augmented opportunities for contact with the growing number of unhospitalized active cases in the adult population.

Results of Starvation Upon Size and Growth. That children thrive poorly during underfeeding or famine is a truism requiring no substantiation from authority. Of the many reports from the World War experience only a few will be cited. Davidsohn[15] presented data on physical measurements of orphanage children in Berlin, contrasting 300 youngsters of 1908–09 with a comparable group from the same institution in 1919. The study showed that the 1919 boys weighed 15% less and were 7.2% shorter, while the girls weighed 24% less and were 6.4% shorter. Expressed in chronologic terms the boys of 1919 corresponded in size to boys $1\frac{1}{2}$ years younger of peacetimes, and the girls corresponded in size to girls $1\frac{1}{4}$ years younger. Interestingly in Davidsohn's group of children the weight was affected adversely to a greater degree than was the length, whereas in Pfaundler's[41] series the opposite relationship was encountered. In Munich[41] 2500 children entering school in 1917–18 were measured and the data compared with those for 1912. The average weight of the children was found to be 4% less than before the war, the height 7% less. The differences were especially noteworthy among children from the better social classes. Kaup[27] studied an elder age group in the same city (Munich). He compared the measurements on over 100 boys 14 years of age in 1920 with the data on a similar group obtained in 1913. At the later period the length difference averaged −2.2 cm. (1.4%), the weight averaged −1.5 kg. (3.8%). The deficit in length for these older children was thus relatively less than had occurred with Pfaundler's more youthful population sample.

Will children after being starved for several years always be smaller than their normal contemporaries, or will the temporarily slowed growth impulse accelerate to correct for the deficit once a liberal intake of food is provided? A partial answer to this question lies in the observations on the excellent nutritional response of war-stricken European children to good food and hygiene after the war. From 1919 through 1921, with the aid of financial contributions from all over the world hundreds of thousands of semi-starved youngsters were sent to more favorable environments for recuperation and upbuilding. Scores of reports testified to the rapid recovery, sudden growth and restoration of visible signs of good health. For example, Abderhalden[1] described a group of 27 Austrian children aged 8 to 14 years received in Magdeburg. In 8 weeks the average weight gain was 3.2 kg. and the average height increase was 2.8 cm. Bloch[6] reported on 30 severely undernourished children sent from Halle, Germany, to Rickenbach, Switzerland. In a little more than a month these put on weight averaging 5.3 kg. (11.7 pounds) and the hemoglobin had climbed more than 10 points in mean value, ranging from 38 to 61 on admission

and between 54 and 72 on discharge. Analysis of Reischl's[44] figures on 1543 Austrian children sent to neighboring rural camps for 1 to 2 months reveals an average gain of 0.3 kg. per week. When one recalls that the rate of weight gain for normal healthy American children amounts only to about 0.05 kg. weekly,[22] the spectacular growth curves of Europe's children are eloquent evidences of the state of nutritional depletion of their tissues and the beneficial effect of more favorable diet. Further corroboration is found in the reports of Schlesinger[49] and Rössle and Bönning[45] that by 1923 most of the weight and length deficits in children of school age had become corrected and compensated.

Wolff,[58a,b] school medical officer in Berlin until the Nazis took over, reviewed with careful statistical technique his measurements of the children entering and leaving the school system over a 20 year period, in order to ascertain whether those born during the lean years of the war showed any signs of permanent physical retardation. The mothers of these children had been in poor nutrition during their pregnancy and breast nursing periods, and the children themselves had failed to receive adequate diets during the first few years of life. When they first came to school at the age of 6 years (in 1924–26), both the boys and the girls were 2.5 to 4.0 cm. shorter in average height than were those of the same age who entered in 1927–1928. The weights showed a similar difference of 0.5 to 1.0 kg. in favor of the later born. The gross difference between the means of the entrance in 1924 and in 1932 ranged from 5.9 to 6.5 cm. in height and from 1.07 to 1.57 kg. in weight. These values were shown by calculation to be statistically significant.

Wolff studied these same children 8 years later when they were 14 years old and graduating from the school. At this age the mean weight and height proved to be in the same range as the values for graduates in the years immediately preceding, which were taken as normal controls. Thus by puberty the group of children born during the period of extreme food shortage had caught up with and corrected their growth deficit which had been still detectable at 6 years of age.

The Pirquet System. No review of child feeding in relation to malnutrition would be complete without a reference to the Pirquet system[13,21,43,47,49,50] even though it is now essentially of historic interest. For when World War I was over this system under von Pirquet's direct supervision became an integral element in the administration of food relief to the children of the Central Empires, some 420,000 in all, and stimulated critical discussion all over the world. There were four principal features. The first took 1 cc. of breast milk of composition 3.7 % fat, 6.7 % sugar and 1.7 % protein (energy value 0.67 cal.) as the elemental unit of food value against which all other foods could be measured. The name given this unit was the "nem" (Nahrungs-Einheit-Menge). Tables were prepared expressing common foods in terms of nems or multiples thereof, named by neologisms such as decinem and hektonem. In the relief kitchens which supplied supplementary meals to the undernourished children the food needs of the expected individuals were estimated and added, and then menus prepared to meet the total number of nems required. Each child's portion contained the exact calculated amount of food. Each child ate his complete portion, and there was no waste.

Theorizing that food absorption was proportional to intestinal surface area, and that this in turn was proportional to sitting height, Pirquet proposed that the square of the sitting height be taken as the physical measurement most indicative of the child's nutritional needs. Food re-

quirements could be reckoned in terms of nems per Si^2 (sitting height), with specific allotments made for minimum metabolic needs and for growth, fat deposit and muscular activity.

The third feature was a new index of the state of nutrition termed "pelidisi." This was derived by taking the cube root of 10 times the body weight in grams, dividing by the sitting height in centimeters and multiplying by 100. The range from 90 to 94 pelidisi was interpreted by Pirquet as average, below 90 undernourished and above 94 well nourished. The children of the various Austrian provinces were all measured in these terms and comparisons drawn between their nutritional status before and after receiving food relief.

The fourth feature standardized the subjective or clinical evaluation of the child's nutrition in terms of the coined word "sacratama." The results of the physical examination were described under the consonantial headings of *s*anguis (blood), *c*rassitudo (fat), *t*urgor and *m*uscularis, with the vowels used as symbols to denote deviations from normal, and a code of numbers to summarize these already condensed derivations. The lack of uniformity of assessment among groups of experienced physicians led even Pirquet to admit that this subjective approach was not very accurate or useful.

As Faber[17a,b,c] and others pointed out, grave doubts as to scientific validity attend most of the basic propositions. Sitting height will fluctuate with the state of contraction of the gluteal muscles.[19,20] Pelidisi reflected slight variations in length with much more emphasis than it did appreciable changes in weight. The many neologisms caused confusion. The nem seemed to be no advance over the more familiar calorie, and the resemblance of the pelidisi series to the percentage scale was confusing and misleading. The Pirquet system was judged brilliant but imperfect by the many clinics which gave it a trial, and the familiar height-weight tables retained as being more practical and trustworthy.

Effects of the Current War. At this writing children all over the world are experiencing every kind of deviation from normal ways of living due to war. In some countries such as Russia, China and other dominated territory these changes and hardships are much more extreme than in others more removed from the actual battle areas. That their physical, nutritional and psychologic conditions will be influenced goes without saying, but years must pass and data and critical evaluations accumulate before a comprehensive and historically sound analysis of this war's effect upon child health can be prepared. The lay press has featured innumerable articles on the conditions of Europe's children[14a] but medical reports to date have been relatively few.

Wattie[57] summarized the public health situation in Glasgow during 1941, and the report merits attention as being no doubt somewhat representative of conditions obtaining in other British cities. Infant mortality has been rising, the rate being 93.1 in 1938, 82.7 in 1939, 109.2 in 1940 and 131.5 in 1941 (data calculated for the first 6 months of each year). Analysis of the data showed this rise to be due in large measure to a growing number of deaths from maturity and from congenital malformation. Pneumonia, bronchitis and pertussis were on the increase. It is interesting that, following the enemy air raids on Glasgow during March and April 1941, a great number of cases of whooping cough were reported, the children having contracted the disease while congregated in air raid shelters night after night. Scabies, diphtheria and cerebrospinal fever were unusually widespread. On the psychologic side comes the report that the great

majority of small children have gone through the period of intensive bombing without any neurotic symptoms or similar ill-effects. With the older children more juvenile delinquency was being observed, the increase in convictions being about 40%. This figure represents about 2% of the whole age group. Home discipline is lax because many fathers are in military service and mothers occupied with war work, and the schools have been functioning on a part-time basis.

The British government is taking special steps to maintain good nutrition among children. Provision has been made for outdoor camps and extra milk, fruit juices, hot breakfasts and good lunches at school. English children, especially those from the slums, show marked benefit from the government's program.[8] Mackay[34] found an increase in borderline anemia in slum children. Milligan and Lewis-Faning[37] studied the growth and physical strength of 133 boys 11 years old in Glossop from January–February to September 1941, and found that the growth in weight was 48% and in height 79% of pre-war standards. Payne and Topley[40] studied 27 children in a base hospital by the vitamin C saturation technique and noted that 14 were markedly lacking this vitamin. Harris,[23] using a similar technique, compared data from school children in the spring of 1941 with the vitamin C status of children of the same age and social background in the spring of 1939. An appreciable drop in the saturation level was detected and attributed to the diminished supply of available fresh fruits.

Stuart[53] and Stuart and Kuhlmann[54] have published a model report on child health conditions existing in southern France in the first 6 months of 1941. They studied the children of Marseilles by the most modern scientific methods, collecting anthropometric, roentgenologic, laboratory and dietary data to serve as a base line from which to measure the progress of these children's growth under the restrictions and handicaps of war conditions. There were approximately 200 children under 2 years of age in the random sample studied, on diets most of which had been deficient in vitamins, animal proteins and calcium for a year preceding. It had been planned to reëxamine the children at 6 months' intervals to note the irregularities and disturbances which might develop, but the turn of circumstances occasioned by the recent German occupation of all of France presumably has halted the work on this project. Stuart and Kuhlmann published the data of the initial survey, recording body weight, size in terms of recumbent body length, standing height, chest circumference and pelvic breadth measurements, and muscular and osseous development as measurable by the roentgenogram. In comparison with the accepted standards for normal American children of equal age, the French children were found a little smaller and of short and stocky build. The data for body weight did not support the view that any large proportion were underweight to a marked degree, though the absence of any previous examination made it impossible to determine whether their rate of growth had been slowed during the months preceding the survey. A far greater irregularity obtained in the patterns of bone calcification then would be expected normally, and this was attributed to environmental factors. Mild to moderate rickets was found in 13 of 27 infants under 22 months. Failure of these babies to receive a vitamin D supplement was not primarily a result of war but rather was due to the absence of any antecedent national public health program of education of mothers in the principles of infant care and welfare. No roentgenographic or clinical evidences of scurvy were encountered despite the frequent findings of very low concen-

trations of ascorbic acid in the blood samples from these children. Other studies, not as yet reported, indicated that the reserve stores of food substances had been greatly depleted. The authors concluded that the deprivations of important foods had not been going on for a long enough period of time nor had been great enough in amount to lead to clinical disease, but with continuation of unfavorable conditions for another year open manifestations of disease could be expected to become more and more frequent.

Despert[15a] recently published a preliminary survey of children's reactions to the present war. In this review she carefully evaluated the psychiatric bibliography reports of the past few years, both foreign and American, and presented some personal observations on a group of New York children. The impression is gained from the British reports that the mass evacuation of 1,500,000 mothers, children and physically handicapped individuals from London early in the war resulted in widespread psychologic maladjustments and anxiety states. Most observers agreed that the harmful effects of evacuation were worse than the "raid-shock" of blackouts and bombings. The main source of difficulty was the separation of children, especially the younger ones, from their parents. In the absence of control data on symptoms existing prior to the war, it is difficult to properly evaluate the significance of behavior disturbances manifested by the children in the evacuation camps and foster homes. The most prevalent complaint was enuresis. Whether or not delinquency increased remains a moot point. An increase in restlessness and irritability especially in the pre-school age group was reported. Despert describes Brander's[7a] contribution on evacuation and air-raids and their immediate and after-effects on Finnish children during the Russo-Finnish war of 1939–40. Agitation, claustrophobia, night terrors, stereotypies, tics and enuresis followed the bombings. Even when there were no bombings the continuous air-raid alarms gave rise to persistent tension and an insufficient amount of sleep, which caused the children to exhibit symptoms of nervousness. The children's reactions during raids were greatly influenced by the behavior of the people about them. Six months after the war Brander made an attempt to evaluate the reactions of the children to the war. He found that any stimulus which would recall the war elicited psychogenic reactions and neuropathic symptoms. War was reflected in the games of the children. Though there were very few cases of serious psychiatric disorders attributable to the war experience, he concluded that profound changes had taken place in the Finnish child's psychic life as a consequence. In Despert's observations on American children, in every case in which parents reported anxiety in relation to the war the child was found to have presented previously an anxiety problem. Children in the United States have not been subjected to the violent experiences of their European cousins nor do they exhibit symptoms of profound psychic trauma.

Medical Relief. Mackenzie[35] and others[14] have been emphasizing the delay at the close of the last war in getting aid to the conquered countries with confusion and costly overlapping among the various relief organizations. To avoid a similar tragedy in the years to come, it is imperative that in the central administrative program for post-war reconstruction there be set up effective coördinating machinery for administering proper medical relief as promptly as feasible.

To the Reviewer it seems that opportunity should be provided within the relief organizations for the scientific investigation as well as treatment

of malnourished and disease-ridden childhood populations. From the study of such war-sick children can come a clearer understanding of the countless physiologic mechanisms at work within every child, and the relative effectiveness of various prophylactic, nutritive and curative agents in current professional use can be subjected to comparative analysis. If the supervision and practical management of medical relief for the childhood fraction of stricken people were entrusted to skilled pediatricians, not only would these children receive excellent attention but the clinical material could serve for the elucidation of lessons of significance for all children of the future.

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GYNECOLOGY AND OBSTETRICS

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NAUSEA AND VOMITING OF PREGNANCY

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The Scope of the Problem. During the first trimester of pregnancy about one-half to two-thirds of women experience some degree of nausea and vomiting. This can be considered severe, however, in only about one-third of the patients[13] and necessitates hospitalization in approximately 1 out of 150 private patients.[27,45] Among those attending clinics the incidence is considerably less, varying from 1 in 400[45] to 1 in 800.[27] In Denmark (population 3.7 million, 65,000 births annually) hyperemesis gravidarum accounts for about 6 deaths and 30 to 40 therapeutic abortions a year.[4]

Apparently neither color, age, race, parity nor marital status have any bearing on the occurrence of hyperemesis,[16,40] although it is said to have an earlier onset and run a longer and more severe course in primiparas.[20] Fewer cases have been reported from Germany and England than from the United States and France,[9] but hyperemesis is practically unknown in the Oriental countries with the exception of Japan. This occurs in spite of the fact that Oriental women live, according to our standards, under very unsanitary conditions, and exist on a diet which is deficient in vitamins A and B and calcium. Also, such conditions as cystitis, nephritis

and pyorrhea, which are frequently incriminated as foci of infection, are found much more commonly among these women than among those of the Occident.[58]

It is generally agreed that hyperemesis complicates only the pregnancy of human beings. Numerous attempts, however, have been made to reproduce it in lower animals such as dogs and cats.[20,37]

Clinical Picture. Although some authors[44] state that three-fourths of patients begin to vomit before the first missed period, most clinicians consider that the usual onset is about the 6th week. The condition may last only a few weeks or extend over a period of 2 to 3 months,[54] but generally the woman is symptom-free[9,13] by the beginning of the second trimester. The severity varies from a slight feeling of nausea on arising in the morning and distaste for food, to a condition of severe dehydration and emaciation and apparently toxemia.

The term "toxemia" should be employed with considerable caution because as yet no specific toxins have been isolated, although the clinical and pathologic findings resemble those seen in other toxic conditions.

Pathologic Anatomy. The kidney and liver in fatal cases show cloudy swelling and fatty degeneration; and in addition, centrilobular necrosis may be observed in the liver. Even the picture of acute yellow atrophy has been noted at times.[12] If these findings were confirmed, they would suggest that a toxin was the etiologic agent. Sheehan,[49] however, has been unable to do this. His only consistent finding was that hearts from patients dying of hyperemesis rarely weighed 230 gm.; whereas a heart of this small size was observed rarely in association with ordinary pregnancy. He also called attention to the many symmetrical, pin-point hemorrhages in the corpora mammillaria and thalami resembling those found in Wernicke's encephalopathy, Korsakoff's syndrome and in some other toxic states. In severe cases hemorrhages are noted in the retina.[60,66]

Unfortunately the postmortem findings cannot be taken as conclusive evidence of the presence of a toxin, because they can be explained also on the basis of the cycle of vomiting-dehydration-emaciation-inanition-starvation, once such a cycle is initiated by some factor associated with the pregnant state.[10,49]

The etiologic theories fall into two main groups, the neurogenic and the organic.

Neurogenic Theory. Practically everyone admits the presence of a neurogenic factor; first, because the disease is more prevalent among those women with more leisure time, and among those who, before pregnancy, were regarded as somewhat unstable psychically[4,48] (*a priori* reasoning, perhaps); and second, on account of the excellent response of the condition to psychotherapeutic measures such as isolation and positive suggestion. Atlee[3] has reported on 33 patients whose hyperemesis was handled as a purely neurotic manifestation. Only 4 women failed to respond to this treatment. Two of these (unmarried girls) died of intercurrent pneumonia. The other 2 were aborted therapeutically, and although their fetuses were not actually expelled until 2 days later, vomiting ceased as soon as the patients believed that their pregnancies were terminated. One of these last 2 women responded to psychotherapy for hyperemesis in a subsequent pregnancy.

Atlee's interpretation of hyperemesis is as follows:

> Vomiting of pregnancy is a protest against pregnancy on the part of the unconscious mind—a defense or rejection tendency, directed against what is unconsciously felt as a foreign body, but displaced (in the psychological sense) and carried out

in regard to the gastric contents. Only in the second half of pregnancy, when the movements of the child no longer permit even the hysterical woman to deny the genital location of the changes and sensations, does the inclination to vomiting cease . . . . vomiting is a distorted attempt on the part of the unconscious mind to rid the self of the fetus.

To account for the pathologic findings Atlee submits the following points: (1) Laboratory animals dying from starvation or continued loss of gastric juice present the same pictures in their livers as the woman dying from hyperemesis. (2) Starvation sensitizes the liver to poisons. Mental fatigue, undernourishment and use of salvarsan in Germany during the years 1916–20 were associated with an increase in acute yellow atrophy. (3) Mental disturbances *per se* can produce hepatic changes indistinguishable postmortem from those seen in fatal cases of hyperemesis gravidarum. (Cases cited.)

Another reason, advanced in support of the neurogenic theory, is the occurrence of vomiting and similar symptoms among the husbands of pregnant women.[3] Most authorities, however, think the incidence of this phenomenon is too small to be conclusive.[59]

The opponents of the neurogenic theory point out that the majority of women cannot be regarded as psychotic, yet when pregnant the majority do suffer from some degree of vomiting.[28] Moreover vomiting may have its onset before the first missed period or before the woman suspects that she is pregnant.[44] The tendency here is to regard the neurosis as an aggravating factor and very likely one which obscures the true cause.[12,19,30,38,44,64]

Organic Theories. 1. *Those of Paternal Origin.* Aside from his influence on the mental outlook of the woman, the father is incriminated as being responsible for hyperemesis only by the appearance, *via* the fetus, of isoagglutinins in the mother's blood, a mechanism similar to that of the Rh antigen in causing erythroblastosis fetalis.[25,33] This, however, has been proven in only a few cases, and some investigators[25] have even used injections of father's blood to bring an end to vomiting, but their success probably may be ascribed to a non-specific psychotherapeutic effect.

2. *Those of Placental Origin.* Many theories center around a derangement of the placenta as the etiologic agent. One group of French workers[4] believes that pathologic changes in the chorionic villi are responsible for the vomiting. To support this theory these investigators cite cases similar to the following 2: A woman died 14 days after the onset of hyperemesis. She was found to have a hydatidiform mole, the normal course of which is more than 1 month. Another woman who continued to vomit for 26 days after abortion was subsequently shown to have retained a fragment of placental tissue. Ordinarily recovery should occur within 2 weeks at most. There are, however, many such patients who do not suffer from vomiting or any other toxic signs. Obviously, then, some other factor must be at work.

This may be fragments of chorionic villi and detached masses of chorionic epithelium which are found often within the maternal blood-vessels. Peckham[44] postulates that the normal mother can dispose of such foreign bits of tissue satisfactorily, but when the nervous system is upset, as during pregnancy, she is unable to do this—a point difficult to prove.

Another theory is that of Johnson,[26] who says that stasis of blood in the intervillous spaces, if of sufficient duration, leads to degeneration of chorionic tissue and the production of tyrosine. Bacteria and/or enzymes circulating in the blood convert tyrosine to tyramine, and the absorption of the latter is responsible for the symptoms of hyperemesis.

Viet and others[54,63] postulate the presence of a syncytiotoxin, whose source is the placenta, a toxin normally neutralized by a substance called syncytiolysine. For some reason the mechanism fails, and the mother is no longer able to destroy the fragments of villi which are circulating through her body. The symptoms of hyperemesis are produced by the direct action of the toxin on the vomiting center and the vital organs.[20,48] In support of this theory is the evidence that urine from a toxemic gravida must be diluted considerably before it can be injected safely into mice for the Aschheim-Zondek test.[9] Clinically the eye manifestations, *i. e.*, nystagmus and retinal hemorrhage, resemble those found in other toxic conditions.[8,60] There is also a marked similarity of the symptoms of severe hyperemesis to those of the toxic psychoses[6] and of mild cases to the so-called toxemia of amenorrhea.[11] Nevertheless, it still remains for this toxin to be isolated and its source determined.

3. *Those of Maternal Origin.* (*a*) Intercurrent Processes: Vomiting may, of course, be produced in the pregnant woman by any condition which causes the non-pregnant woman to vomit. Such would include tonsillitis,[9] gastritis,[9] appendicitis,[9] cervicitis,[9,52] cholecystitis,[52] peptic ulcer,[52] nephritis,[11] urinary back pressure,[22] the presence of tapeworms,[42] as well as innumerable other causes. Pyelitis,[9,41] hyperthyroidism[16] and avitaminosis[35,36] also will cause vomiting. These three conditions are associated more commonly with pregnancy than the preceding ones, and if they are present in a more or less latent state before pregnancy, the extra demands of the fetus will be apt to make them worse.

A word should be said in regard to avitaminosis-B. Since some of the neurologic signs found in severe cases of hyperemesis resemble those of polyneuritis and Korsakoff's syndrome, the B complex has been thought to play an important rôle in the development of vomiting.[56] Likewise the convulsions, which may be associated with hyperemesis gravidarum but which are seen more commonly in eclampsia, may be correlated with low pyruvic acid levels.[35]

(*b*) Metabolic Derangements: Theories in support of a basic metabolic derangement as the cause of hyperemesis center about the liver for three reasons: (1) Postmortem changes are most marked in the liver. (2) Hepatic function tests (porphyrin and bilirubin elimination, the xanthoproteic test)[23,46] indicate decreased activity. (3) Examination of the blood and urine reveals disturbances of body metabolism associated with hepatic damage.

These biochemical findings[44,45,54,62,65] include increased blood urea nitrogen, acetone bodies, and blood organic acids (uric, amino and lactic) and decreased blood chlorides. The CO_2 combining power varies widely but is generally within normal limits. The van den Bergh test is slightly positive in moderately severe cases. Serum proteins, hemoglobin and red blood cell counts are high as a result of the dehydration and hemoconcentration. The blood sugar usually is depressed, although in severe cases increased values are sometimes found.[44] The urine is loaded with albumin, acetone bodies, and the products of bile pigment metabolism. The ammonia nitrogen coefficient is increased, and this Peckham[44] attributes to starvation.

The glycogen reserve of the liver[19] is decreased either through prolonged fetal demands—at this time the placenta, the great storehouse, is not completely formed[64]—or because the dietetic habits and preferences of the mother result in a decreased carbohydrate intake.[62] Such a prolonged, gradually increasing hypoglycemia may give rise to neurotic symptoms[62]

and will sensitize the liver to the action of toxins. Experimentally it has been shown that less poison is required to kill an animal whose liver has been depleted of its carbohydrate reserve than to kill a normal one.[61] Once vomiting has begun a vicious circle is set up, for continued vomiting further depletes liver glycogen. The intravenous administration of glucose to combat this loss will, in many cases, restore the woman to health[62] and is a fundamental part in the treatment of these patients.

The effects of a deranged carbohydrate metabolism are felt also on other reactions of the body. Sussman[57] has pointed out that the normal response of the body to parathormone is decreased greatly in the presence of liver damage. Ordinarily calcium will relieve the symptoms of CCl_4, phosphorus and hydrazine poisoning whether hypocalcemia is demonstrable or not. A patient with hyperemesis, however, does not cease vomiting when calcium is administered alone, but she will obtain relief if parathormone is given in addition to the calcium.

The ketosis, acidosis and shift in pH observed in these women is linked also to the question of deranged carbohydrate metabolism.[44] In dogs, a disturbance in acid-base equilibrium unassociated with renal injury has been found to produce a toxemic condition.[37]

It is possible that the metabolic disturbance can be explained on the basis of the next topic to be considered.[43]

(*c*) Endocrine Dysfunctions: Due to the rapid development of the endocrine system during the first trimester of pregnancy, almost all of its hormones have been held responsible for hyperemesis. The following are some of the important ones:

Gonadotropin: During pregnancy the anterior pituitary gland increases in size, and from the chromophobe cells new ones develop. These contain acidophilic granules and are known as "pregnancy cells."[5] It is not unreasonable to assume, therefore, that the gonadotropic hormones, as well as those which exert a trophic effect on the other endocrine glands such as the thyroid, adrenal and parathyroid, increase in amount.

Numerous workers have attempted to demonstrate an hyperprolanemia and hyperprolanuria in association with hyperemesis. Data published between 1936 and 1939[7,20,32,47] suggested that the amounts of gonadotropic hormone in the blood of patients suffering from hyperemesis were greater than those present in normal pregnancy. One group of investigators[7] thought that it was able to correlate the level of prolan with an abnormal proliferation of plasmodial elements in the placenta, but subsequent workers[4,53] have not been able to confirm these observations.

Estrogen: Determinations of the amounts of the estrogens in the blood and urine have shown that nausea is associated with low estrin levels,[51] and Hawkinson[20,21] has reported both low estrogen and high gonadotropin values in such patients. Over 150 of these women were treated successfully with estrogenic preparations. Nevertheless synthetic estrogens can themselves produce nausea and vomiting.[18] Smith and Smith[9,50] postulate an abnormal metabolism of estrogens at this time of such a degree that there is an excessive destruction of them.

Anterior Pituitary-like Substance: Subnormal urinary values for APL associated with hypernormal values in the serum have been reported from a small series of cases by some Norwegian workers.[7] These values returned to normal following recovery from vomiting.

Adrenocortical Hormones: One theory attributes nausea and vomiting to adrenocortical failure. The evidence in support of this view is:[4,29]

(1) Normally the adrenal cortex hypertrophies during pregnancy, but in fatal cases of hyperemesis, it is found to be atrophic. (2) Nausea and vomiting are the first symptoms in adrenalectomized animals. (3) Anorexia, nausea and vomiting are the first symptoms of Addison's disease. (4) Biochemical findings in hyperemesis and Addison's disease are similar. (5) Treatment with adrenocortical extracts will terminate vomiting.

In comment on this last point, it should be pointed out again that the therapeutic effects are very difficult to evaluate because of the strong susceptibility of the condition to psychotherapy. Bandstrup[4] says, "When an effect is obtained it seems reasonable to look upon it as a palliative and compensatory (measure) through increase in the liver glycogen and blood cholesterol, that is, a treatment along the line of the glucose-insulin treatment."

Interfunction of Adrenal and Pituitary Glands: Elevation of blood cholesterol, a common finding in hyperemesis,[55,63] suggests a disturbance of fat metabolism, the controlling agent of which is considered to be the ketogenic hormone of the anterior pituitary gland. Cholesterol is said to counteract this secretion and also to neutralize both endogenous and exogenous toxins and to increase liver glycogen.[53,63] Kemp[28] suggests that the liver can function efficiently and maximally only in the presence of an adequate catalyst and proposes that this may be an adrenocortical secretion.

(*d*) Allergy: The rôle of allergy in the production of nausea and vomiting is closely linked with that of the endocrine glands, for the causative agent is considered to be the corpus luteum hormone. There are those[43] who contend that an excess of corpus luteum hormone secreted at the time of conception may be responsible for hyperemesis but the chief reason advanced is that the woman has become sensitized to the corpus luteum hormone through continued absorption during her active sex life. Vomiting appears at the time when corpus luteum is increasing physiologically in size, and stops when the corpus luteum ceases to grow.[24,54] (The proponents of this view point out that the corpora lutei of the pregnant and the non-pregnant woman may not actually be the same, for on microscopic section those of the latter contain more colloid and larger granular cells.) Finch[13,14,15] was able to demonstrate in a large, well-controlled series of patients positive intradermal reaction to an extract of the corpus luteum (not progesterone but an as yet unidentified hormone), proportional in almost every case to the degree of nausea and vomiting the patient experienced. He has found also that patients who have had nausea and vomiting during pregnancy are extremely likely to experience it following the administration of diethylstilbesterol for any other clinical condition for which it may be indicated. These patients all show positive intradermal tests with the corpus luteum hormone. From this he infers that the allergen very likely is some substance produced secondarily by an estrogenic substance such as diethylstilbesterol. Furthermore, desensitization can control the patient's symptoms.

(*e*) Miscellaneous Conditions: In addition to the causes given above, there are a number of others which have been proposed but whose rôle in the production of hyperemesis has not as yet been thoroughly investigated. These include hunger,[54] duodenal spasm,[39] faulty protein digestion,[52,54] achlorhydria,[2,20] reverse peristalsis brought about by hyperemia and growth of pelvic structures,[20] unstable nitrogen equilibrium[31,34,43] and overirritability of the vagus.[54]

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF APRIL 20, 1943

Studies on Gelatin as a Plasma Substitute. I. *Efficacy of Gelatin in Experimental Hemorrhage and Burn Shock.* W. M. PARKINS and J. S. LOCKWOOD (Harrison Department of Surgical Research, University of Pennsylvania). The gelatin used in these studies was produced by alkali hydrolysis of bovine long-bone collagen under controlled and standardized conditions, and was infused as a 6% solution in saline, having a colloid osmotic pressure, after autoclaving, of about 45 mm. of Hg.

Ten unanesthetized dogs subjected to rapid massive hemorrhage to the point of air hunger or respiratory failure, with blood pressure reduced to about 20 mm. of Hg, all survived when immediately infused with a volume of saline or gelatin equivalent to the amount of blood withdrawn (approximately one-half their blood volume). The maintenance of a higher total protein concentration in the 5 gelatin infused dogs, the considerably greater increase in plasma volume, and the return of the blood pressure to normal range 15 minutes after infusion, in contrast to the response of animals to saline, indicates a definite superiority of gelatin over saline in this type of experimental hemorrhage.

Dogs anesthetized with nembutal, subjected to hemorrhage of 30 cc. per kg., and infused with gelatin were better able to tolerate subsequent repeated hemorrhages of this amount than animals infused after each hemorrhage with saline.

Sixteen dogs under nembutal were subjected to a standard procedure of slow 3-stage hemorrhage with blood pressure maintained at 30 to 40 mm. Hg for 30 to 40 minutes. Three untreated animals succumbed within 2 to 5 hours. Two of 5 saline-infused animals slowly recovered and 3 died within 6 hours. In 5 gelatin-infused animals the increase in plasma volume was more marked than in 3 plasma-infused dogs. In the gelatin-infused dogs the blood pressure was as well restored and maintained as in the animals receiving plasma. All gelatin and plasma-infused dogs made a rapid and uneventful recovery.

Treatment of anesthetized dogs subjected to a standard reproducible body burn yielded the following results: All of 5 control animals died; 3 of 5 saline-treated animals succumbed with uncontrolled hemoconcentration; 1 of 4 plasma-treated dogs died, and 7 of 8 gelatin-treated dogs failed to survive in spite of a correction of hemoconcentration of the same degree as that obtained with plasma. Although gelatin treatment extended survival well beyond the period when death associated with hemoconcentration occurred in controls, the gelatin-treated dogs showed a progressive decline in blood pressure without significant reconcentration. Since gelatin is capable of compensating for the osmotic pressure of the lost plasma protein, there is reason to expect that the effectiveness of gelatin therapy in burns may be enhanced by modifying the composition and technique of administration of gelatin, and by the concomitant administration of certain humoral factors.

II. *Observations on Toxicity and Elimination of Gelatin.* C. E. KOOP, CECILIA RIEGEL, H. M. VARS, H. L. RATCLIFFE, W. M. PARKINS and

J. S. Lockwood (Harrison Department of Surgical Research and Department of Pathology, University of Pennsylvania). Studies on the toxicity of intravenous gelatin as a plasma substitute were undertaken after single and repeated infusions of 10 to 30 cc. per kg. of 6% gelatin solution.

Glucose tolerance, serum protein, albumin and globulin, non-protein nitrogen, and prothrombin determinations revealed no liver damage. Fibrinogen levels were decreased. Bromsulfalein retention was marked 3 hours after infusion, diminished at 24 hours, and normal at 48 hours. The degree of retention became increased and the return to normal increasingly delayed as the number of weekly infusions increased. Similar but less marked retention was observed in dogs infused with plasma.

Kidney function as determined by urea clearance was unimpaired.

There is no evidence that gelatin *per se* is pyrogenic in the dog. Repeated infusions varying in amount, number and frequency failed to produce allergic reactions.

Sedimentation rates, corrected for hematocrit changes, showed a two- to fourfold increase after infusion, with return to normal as the gelatin disappeared from the blood.

Clotting time was increased 16% 15 minutes after the start of infusion, 30% at 3 hours, and returned to normal within 24 to 48 hours.

Following gelatin infusion diuresis and relatively rapid excretion of gelatin occurred which decreased after 6 hours following infusion. Not all of the gelatin which disappeared from the blood was accounted for by urinary excretion. The fate of the remainder is obscure. Plasma proteins fall rapidly after infusion and were replaced at about the same rate at which gelatin disappeared from the blood. Gelatin was present in only minute quantities after 5 days. A decrease in total plasma protein concentration which occurred soon after infusion may be explained by increase in plasma colloid osmotic pressure.

In the normal dog, repeated infusions of gelatin over long periods of time were not accompanied by demonstrable tissue damage, except for capillary hemorrhages in the adrenal glands which were visible for only 48 hours after the infusion. In those animals where gelatin was given as a blood replacement there was evidence of protein leakage in the kidney tubules and minor degeneration in liver and kidney in 24 hours. These changes, only slightly more marked with gelatin than with plasma, were apparently reversible.

Further Studies on the Mode of Action of Sulfonamides. M. G. Sevag, Jane Henry and Ruth Richardson (Department of Bacteriology, University of Pennsylvania). The results of our studies show that proteins compete with bacterial enzyme proteins for sulfonamides, *e. g.*, neopeptone reverses the inhibition of the respiration of bacteria by sulfonamides. The reversing effect of neopeptone, contrary to Lockwood's postulates, is not due to acceleration of the metabolic activities of bacteria but due to a competition with bacterial enzymes for sulfonamides. This competition is effective when the amount of neopeptone is in excess of the amount required for optimal acceleration of the metabolic activities of bacteria. Similar competitive effects are observed also when the inhibition of the carboxylase activity of *E. coli* by para-, meta- and ortho-aminobenzenesulfonamides are measured in the presence and absence of proteins. In the absence of proteins the 3 isomers exercise similar inhibitory effects. On the other hand in the presence of an appropriate amount of neopeptone

or human serum albumin, the para-isomer maintains its inhibitory effect, but the meta- and ortho-isomers show no inhibitory effect. The latter 2 isomers show, therefore, greater affinity for these serum proteins than for the bacterial enzyme proteins involved. p-Aminobenzoic acid reverses the inhibition of the respiration of bacteria by sulfonamides (50% to 100% reversal). p-ABA likewise reverses the inhibition of bacterial carboxylases by sulfathiazole. These and other facts show that the action of sulfonamides is directly related to the blocking of the respiratory enzymes of bacteria. (Sevag, M. G., and Shelburne, M., *J. Bacteriol.*, **43**, 411, 421, 447, 1942; Sevag, M. G., Shelburne, M., and Mudd, S., *J. Gen. Physiol.*, **25**, 805, 1942.)

Clinical Studies on Incoördination of the Circulation. ISAAC STARR (Research Department of Therapeutics, University of Pennsylvania). The change in the circulation when the subject arose, as determined by the ballistocardiograph, has been employed as a test of circulatory coordination; *i. e.*, of the ability to adapt its volume to the needs of the moment.

Normal standards were determined by a statistical analysis of the results of 120 tests made on 75 normal subjects. Abnormalities were sought in 200 tests made on 150 ambulatory hospital patients.

In healthy persons the amount of the circulation per minute changes but little when they arise. In a large percentage of sick persons the circulation, on arising, changes much more than in healthy persons. In the common abnormality the circulation after arising is unduly increased; in the far rarer type it is unduly diminished.

Incoördination of the circulation is a very common clinical condition and this may account for the widespread occurrence of symptoms such as dizziness, faintness and shortness of breath, which so many of these patients exhibit.

BOOK REVIEWS AND NOTICES

THE EMBRYOLOGICAL TREATISES OF HIERONYMUS FABRICIUS OF AQUAPENDENTE. THE FORMATION OF THE EGG AND OF THE CHICK. THE FORMED FETUS. A facsimile edition, with an introduction, a translation, and a commentary by HOWARD B. ADELMANN, Professor of Histology and Embryology, Cornell University. Pp. 883; 85 figs. Ithaca, N. Y.: Cornell University Press, 1942. Price, $12.00.

THE translation of these two important embryological treatises—apparently for the first time in any modern tongue—and their facsimile reproduction from the most reliable editions constitute a noteworthy event in medical historical achievement in this country. Further value is added by the 121 pages of the scholarly preliminary matter on the "colorful" life of Fabricius and the history of embryology before Fabricius' time, together with an analysis of the two embryological treatises, and inclusion of the unique supplement of 10 leaves of explanatory matter accompanying the colored plates bound in the copy of *De Formato Foetu* that is in the Library of the College of Physicians of Philadelphia. The spelling of Fabricius' birthplace without the "c" in the title and with it in some places, as on page 6, merely reflects the frequent variation that is found on this point. A similar explanation must serve for the confusion about dates of printing *De Formato Foetu*. The author explains (p. 122) the different dates used in title page, colophon and dedication and his reasons for preferring the 1604 of the colophon.

To the tyro in medical history the name of Fabricius perhaps first recalls three items: his construction of what was perhaps the first permanent anatomic theatre, in Padua, and his chief contributions to medical progress—the recognition of the valves of the veins and as the teacher of Harvey at Padua. His influence as a teacher and investigator was undoubtedly an important factor in stimulating his more brilliant pupil toward his synthesis of the circulation of the blood. Less well known, however, are these embryological treatises, which also stimulated Harvey, by his own acknowledgment, to the construction of his second great work. Dr. Adelmann's evaluation of Fabricius' contribution steers a middle course between the extremists who see in Fabricius anything from the leading figure in a period full of leaders, on the one hand, to a traditionalist "blinded to facts staring him in the face" (Foster). Rather does Adelmann look on Fabricius the embryologist as a strong and intelligent observer and pictographer, a proponent of useful classifications and tools of expression; but one who, as a child of his times—such as Harvey himself was—bowed occasionally too low to authority and to the dead hand of Galen. Fabricius, of course, made errors of observation and interpretation, some of which were picked up by his pupil, Harvey, who in turn made the same sort of errors. But how could anything else be expected, given the complexity of the subject, the fragmentary basis of the scientific knowledge of the day, and the lack of suitable instruments permitting more precise study? He should be regarded as a follower of Aristotle only partly freed from the fetters of omnipotent tradition. Fabricius' position among the great in anatomy and embryology is clarified and enhanced by Adelmann's work.

Hearty congratulations are in order to the American Council of Learned Societies for aiding financially in the publication of the volume, to the Cornell University Press for the excellent, and yet not over luxurious format, and above all to a busy Professor of Anatomy and Embryology whose enthusiasm for books and their contents enables him to bring his task to a successful completion in these difficult times.

E. K.

THE MEDICAL CLINICS OF NORTH AMERICA (Vol. 27, No. 1, Chicago Number, January, 1943. Pp. 267; illus. Philadelphia: W. B. Saunders Company, 1943. Price, year $6.00.

MORE than once Sir William Osler, suggesting the way to Aequanimitas, indicated that physicians would do well to compose themselves for sleep by perusing volumes far from the field of medicine. That advice gently put forth, in more leisurely days of course, can stand the test of time; but in these strained days, when physicians practising general medicine must be rationed and their time packed with consultations to the exclusion of their regular medical reading, this number of the *Medical Clinics of North America* will be welcomed by them. It has proved to be a stimulating bedside companion to be read profitably, perhaps an article at a time, without unduly exciting the resting physician.

The present number is chiefly devoted to gynecologic problems, but, as usual, includes other topics, chiefly on diagnosis and treatment. V. R.

DISEASES OF THE SKIN. By OLIVER S. ORMSBY, M.D., Rush Professor of Dermatology, University of Illinois; Attending Dermatologist to the Presbyterian Hospital of Chicago; etc.; and HAMILTON MONTGOMERY, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research Graduate School, University of Minnesota, Rochester, Minn.; etc. Pp. 1360; 654 figs. (6 colored plates). Sixth ed. Philadelphia: Lea & Febiger, 1943. Price, $14.00.

IN this edition, long a most distinguished example of the best American tradition in the field, Dr. Ormsby is again fortunate in the choice of his collaborator. Dr. Hamilton Montgomery, of the Section of Dermatology and Syphilology of the Mayo Clinic, is an able clinician and competent pathologist. He has, singly or in collaboration, made intensive studies on a number of the complex phases of dermatology. His collaboration with Dr. Ormsby is especially evident in the section on the diseases of metabolism (xanthoma) and in his additions to the paragraphs on pathology which the previous collaborator, Dr. W. C. Finnerud, had revised in the two preceding editions.

The authors have added descriptions of 22 diseases not previously dealt with in the text. The illustrations are generally good but some represent far from typical examples of the dermatosis under consideration.

The text is concise, systematic and up-to-date. The reader is supplied with adequate recent bibliography as well as with some of the classic references.

There are but few adverse criticisms one can make of this book. The section on syphilis, however, is somewhat weak, and, except for the dermatologic aspects, cannot be regarded as adequate for a full understanding of the disease. Certain minor errors, such as placing a discussion of sobisminol (page 960), a bismuth preparation for oral use, in the section on mercury, are inevitable in so large a book as this.

The Reviewer believes that Ormsby and Montgomery's revision of Ormsby's *Diseases of the Skin* is to be highly recommended for medical students and practitioners. H. B.

THE BIOLOGICAL ACTION OF THE VITAMINS. A Symposium. Edited by E. A. EVANS, JR., Associate Professor of Biochemistry, The University of Chicago. Pp. 227. Chicago: The University of Chicago Press, 1942. Price, $3.00.

IN connection with the Fiftieth Anniversary Celebration of the University of Chicago, the Universities of Wisconsin and of Chicago arranged a symposium on the vitamins. One group of papers was presented at meetings held in Madison, Wis., and has been published under the title "The Respiratory Enzymes." The present volume includes the papers presented at the Chicago meeting. Following a general discussion of the title topic by C. A. Elvehyem,

there are stimulating discussions of a number of the vitamins by the foremost chemists, physiologists and clinicians working in this field. While all the papers are noteworthy, 3 are of special interest to those who have followed the progress of research in vitamin chemistry and physiology: the *Biotin* story related by du Vigneaud; *Choline*, by Wendell H. Griffith; and, *The Economy of Phosphorus in the Animal Organism*, by Franklin C. McLean. E. W.

CHEMOTHERAPY OF GONOCOCCIC INFECTIONS. By RUSSELL D. HERROLD, B.S., M.D. Pp. 140; a few tables. St. Louis: C. V. Mosby Company, 1943. Price, $3.00.

THE author presents a much needed volume on a subject of great importance, especially in wartime. The treatment with sulfonamides has opened a new era in the handling of gonorrheal patients. Since the introduction of sulfanilamide in 1935, the literature has contained many reports on the effects of individual sulfonamides on small isolated groups of patients. By necessity, such reports are of importance in the early evaluation of the drugs as they are presented. Herrold presents an experience derived from observing many hundreds of patients treated with various substances. He covers all phases of the approach and method of therapy of gonorrhea with sulfonamides.

The book is complete and readable. It should be available to all physicians treating gonorrhea. L. LaT.

THE FOOD YOU EAT: A PRACTICAL GUIDE FOR HOME NUTRITION. By SAMUEL GLASSTONE, Professor of Chemistry, University of Oklahoma, and VIOLETTE GLASSTONE, University of Oklahoma, Norman, Okla. Pp. 277; 18 illus. Norman, Okla.: University of Oklahoma Press, 1943. Price, $2.25.

BECAUSE perhaps of the wartime shortages and rationing of foods, public interest in this subject and its relation to good health has been greatly accelerated. This book is therefore appropriate at this time and gives the intelligent layman a readable account of the complex subject of nutrition, digestion, and the preparation of foods. Approximately the first half of its contents is devoted to the physiology of metabolism and food requirements, while the remainder is devoted to a discussion and evaluation of food products and the menu. The Reviewer believes that this book will find a useful place in the home of the concerned housewife; likewise, it answers many of the common food questions received by the practising physician. D. T.

CLINICAL LABORATORY DIAGNOSIS. By SAMUEL A. LEVINSON, M.S., M.D., Director of Laboratories and Pathologist, Research and Educational Hospitals, Chicago; Professor of Pathology and Assistant Professor of Medicine, University of Illinois College of Medicine; and ROBERT P. MACFATE, CH.E., M.S., PH.D., Assistant Director of Laboratories, Research and Educational Hospitals, Chicago; Assistant Professor of Pathology, University of Illinois College of Medicine. Second ed. Pp. 980; 156 illus., 15 plates (7 in color). Philadelphia: Lea & Febiger, 1943. Price, $10.00.

RETAINING their objective of a laboratory text which is relatively comprehensive and yet concise, practical, usable, and arranged to make the facts easily accessible, the authors have brought all data and procedures up to date. Many of the newer procedures, such as those for the Rh factor, sulfonamides and phosphatase, have been added, and the text has been enlarged and certain non-essential portions deleted. This volume remains, in the Reviewer's opinion, one of the best in print, triply as a text for students, quick reference book for practitioners, and laboratory manual for technicians and clinical pathologists. M. F.

ANNUAL REVIEW OF BIOCHEMISTRY, VOL. XI. Edited by JAMES MURRAY LUCK. Pp. 736. California: Stanford University, 1943. Price, $5.00.

THIS review is along the same general lines as the previous volumes. Many of the same subjects are reviewed such as chemistry and metabolism of carbohydrates, fats and proteins. There are the usual two chapters on vitamins, one on biologic oxidations and reductions, one on hormones, and so forth. As usual, a few subjects less frequently reviewed or reviewed for the first time have been included. Among these may be mentioned the chapters on The Chemistry of Visual Substances, Avian Biochemistry and Plant Tissue Cultures. In spite of the war several foreign authors have contributed to this review and the usual high standard has been maintained. J. J.

PSYCHOLOGY YOU CAN USE. By WILLIAM H. ROBERTS. Diagrams by JAMES MACDONALD. Pp. 246. New York: Harcourt, Brace & Co., 1943. Price, $2.00.

THE extremely simple, almost monosyllabic language in which this book is written goes a long way toward accomplishing the purpose for which it was written. Fundamentally, it is a semiscientific introduction, for the layman, of the *science* of psychology. The popular conception of psychology as being a study in "How to Win Friends and Influence People" is exploded. Instead, the author gives clear, definite concepts of the importance of this science; why and how concrete reactions and stimuli affect the body and the mind and make the individual react as he does. It is the explanation of behavior and experience in a physical environment—much as a plant is studied in its physical surroundings, or any other living organism.

This book can be recommended to the general lay public as a simple, scientific explanation of a science that still is clouded with a lot of fancy mysticism. E. F.

ENDOSCOPIC PROSTATIC SURGERY. By ROGER W. BARNES, M.S., M.D., F.A.C.S., Professor of Clinical Urology, College of Medical Evangelists; Chief of Urology Service, White Memorial Hospital and Out-Patient Clinic; Senior Attending Surgeon, Los Angeles County Hospital. Pp. 235; 104 illus. St. Louis: C. V. Mosby Company, 1943. Price, $6.00.

THIS contribution is a much needed treatise on endoscopic prostatic surgery. The information presented could be obtained only by an exhaustive review of the literature, as well as wide personal experience.

Anyone having done endoscopic prostatic surgery realizes that the technique is not one that can be mastered by the study of any book. However, much trouble may possibly be avoided by following the suggestions that Dr. Barnes presents. This book should be available to every student of urologic surgery, as well as to those who have any part in the care of prostatic patients. L. LaT.

THE PRINCIPLES AND PRACTICE OF WAR SURGERY WITH REFERENCE TO THE BIOLOGICAL METHOD OF THE TREATMENT OF WAR WOUNDS AND FRACTURES. By J. TRUETA, M.D., Formerly Director of Surgery, General Hospital of Catalonia, University of Barcelona; Assistant Surgeon (E.M.S.), Wingfield-Morris Orthopædic Hospital, Oxford; Acting Surgeon-in-charge, Accident Service, Radcliffe Infirmary, Oxford. Introduction by OWEN H. WANGENSTEEN, M.D. Pp. 441; 144 illus. St. Louis: The C. V. Mosby Company, 1943. Price, $6.50.

THE author's extensive experience in the Spanish Civil War has given him definite and enthusiastic opinions regarding the value of the closed plaster method of treatment for compound fractures. He has adapted and modified

this method, which has been most widely known in this country as the Orr method, for use in many types of injury.

The book is quite didactic and very readable. Some readers may be unable to agree with certain of the statements on physiological and biochemical subjects; for instance, "Blood pressure is the essential factor in the intensity of shock, and everything else must be related to it" (p. 133), or the statement in regard to burns, "Glycogen is often given off by the liver producing hyperglycemia and acidosis . . . ."

The book is absorbing to read and presents a large amount of most valuable clinical experience. The fact that it is based on experience gained in the management of the casualties of modern warfare would seem to make it of great practical value today. J. R.

AN INTRODUCTION TO BIOPHYSICS. By OTTO STUHLMAN, JR., PH.D., Professor of Physics, University of North Carolina. Pp. 375; many figs. and tables. New York: John Wiley & Sons, Inc., 1943. Price, $4.00.

THIS book is intended to meet "the increased demands for physics by students whose primary interests lie in the biological sciences." The principal topics covered include Roentgen rays, radio-activity, biologically active light, vision, auditory mechanisms, structure and properties of surfaces and membranes, and nerve conduction.

The physics discussed largely concerns the instruments and methods employed rather than the physical analysis of the properties of the biologic systems themselves. There is an extensive discussion of the physics of various kinds of radiations including artificial radio-activity. The optical system of the eye and mechanics of sound transmission in the ear are discussed. There is a chapter on the compound microscope and the electron microscope including the formulas for magnetic and electric focusing of electron beams. There is also an analytical consideration of electron deflection in the cathode-ray oscillograph. A generous bibliography is provided for each chapter, and a series of problems offered at the end of the book. M. L.

BIOCHEMISTRY AND MORPHOGENESIS. By JOSEPH NEEDHAM, F.R.S., Sir William Dunn Reader in Biochemistry, and Fellow of Gonville and Caius College, Cambridge. Pp. 785; 328 illus. (4 of which in color). Cambridge: The University Press. New York: The Macmillan Company, 1942. Price, $12.50.

THIS volume follows the author's "Chemical Embryology" (1931), in which the chemical changes going on during embryonic development were presented. Since then a new approach to the problem of morphologic-chemical relationship has developed: namely, an investigation of morphogenetic substances. It is with this subject that the present work is concerned.

The existence of these substances was revealed in the work of Ross Harrison, Warren Lewis, Hans Spemann, and Otto and Hilde Mangold. Since then, attempts to isolate the induction factors has progressed. The book is a stimulating one, written in a clear and understandable manner. Whereas the subject is still filled with irritating gaps in our knowledge, the general pattern of morphogenesis and its chemical background emerges more and more clearly. The work is of importance to everyone interested in the biologic sciences. Its material is significant not only for the biochemist and embryologist, but also for the physiologist and pathologist; it comes as a fresh breeze to subjects somewhat overburdened with purely descriptive morphology. Furthermore, it serves as an introduction to the probable future course of development of the biologic sciences.

The volume is divided into three parts. In Part I the morphogenetic substratum is considered, including such subjects as the constitution of the eggs

of invertebrates and vertebrates, environmental factors and embryonic nutrition. In Part II, the major part of the book, the general concepts of morphogenetic stimulation are presented. Organizers and their specific functions are fully dealt with, as well as the relation of organizers to genes. An interesting discussion of the possible rôle of organizers in carcinogenesis is included. In Part III, the morphogenetic mechanisms are considered: dissociability, heterauxesis, respiration,.metabolism and polarity. D. C.

PROTEINS, AMINO ACIDS AND PEPTIDES as Ions and Dipolar Ions. By EDWIN J. COHN and JOHN T. EDSALL, Harvard Medical School. Including Chapters by JOHN G. KIRKWOOD, Cornell University, HANS MUELLER, Massachusetts Institute of Technology, J. L. ONCLEY, Harvard Medical School, GEORGE SCATCHARD, Massachusetts Institute of Technology. Pp. 686; many tables and figs. New York: Reinhold Publishing Corp., 1943. Price, $13.50.

THIS American Chemical Society Monograph, prepared by such well-known investigators, is a most welcome evaluation of the evidence concerning the size and shape of the molecules of amino acids, peptides and proteins and the number and distribution of the electric charges they bear. The implications considered are of the effect of their charged structure upon their physical properties and their physico-chemical interaction with other molecules.

The fundamental studies of Debye and Hückel, and of Bjerrum serve as the basis for the approach to protein chemistry which is adopted here. From the data collected upon the reactions of the simpler dipolar ions, conclusions and inferences are drawn which are applied in the more complicated study of proteins themselves.

Proteins are highly specialized molecules in which certain general features of structure can be considered as established. Hemoglobin is an excellent example of the relation of specialized biologic function and protein structure. Knowledge of the specific adaptations of other proteins may be expected when the fields of study elaborated in this monograph are explored thoroughly.

Everyone interested in the physical chemistry of proteins will find this volume a necessity. H. V.

VASCULAR SPASM: Experimental Studies. By ALEXANDER JOHN NEDZEL, M.D., M.S., Associate Professor of Pathology at the College of Medicine, University of Illinois, Chicago, Ill. Pp. 151; 161 figs. Urbana, Ill.: The University of Illinois Press, 1943. Price, $2.75.

THIS monograph reviews the literature (with 300 references), and presents the results of an extended series of experiments on the general subject of vascular spasm with special reference to endocarditis, gastric ulcer, liver and kidneys, and multiple sclerosis. Pitressin was used intravenously to produce transient episodes of vasoconstriction in dogs. "Basic disturbances—spasms in vascular beds—appeared in different regions and organs in varying degrees, thus leading to the formation of lesions in widely separated organs. These lesions are bases for different diseases, and yet their etiology is the same." The author concludes that clinically those individuals with highly responsive and unstable vascular beds "have a disturbed splanchno-peripheral balance, their vascular rhythm is easily influenced, and the normal periods of increased tone are readily exaggerated or suppressed in the different regions and organs of the body." Thus the ultimate development of certain disease processes by essentially the same cause. His evidence for endocarditis is quite convincing, while that in the other organs is less impressive but reasonably suggestive. A large portion of the findings are shown in numerous microphotographs.

M. T.

NEUROSURGERY AND THORACIC SURGERY. Military Surgical Manuals, Vol. VI. Prepared and Edited by the Subcommittees on Neurosurgery and Thoracic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 310; many figs. Philadelphia: W. B. Saunders Company, 1943. Price, $2.50.

PART I of this manual is designed primarily for medical officers who have had some training in neurosurgery; but the less specialized physician will find most of the information valuable and necessary in the evaluation of head, spinal cord, and peripheral nerve injuries, as well as certain infections involving the nervous system.

Part II deals with those aspects of thoracic surgery which are primarily the problems of advanced field and dressing stations. The fundamental mechanisms of physiopathology are stated clearly, and the basic principles of diagnosis and treatment are well defined.

No medical officer could be called adequately informed if he did not know most of the content in this manual, whether or not he is capable of acting in the capacity of neurosurgeon or thoracic surgeon. Civilian physicians and students will also find this to be an excellent review. The manual is written in outline form so that any subject can be readily reviewed within a few minutes. T. T.

WAR INJURIES OF THE CHEST. Edited by H. MORRISTON DAVIES, M.A., M.D., M.CH., F.R.C.S., and ROBERT COOPE, M.D., B.Sc., F.R.C.P. Pp. 131; 36 figs. Baltimore: Williams & Wilkins Company, 1942. Price, $2.00.

THE stated object of this small book is "to give in concise form the reasons for and the details of the treatment of the various forms of chest injury met with in warfare." Although the reasons for treatment have been fairly well dealt with, the details have not been well expressed. For the physician who desires in an hour or two to gain a general concept of chest injuries and their management this should serve his purpose well. T. T.

NEW BOOKS

Synopsis of Diseases of the Skin. By RICHARD L. SUTTON, M.D., Emeritus Professor of Dermatology, University of Kansas Medical School; and RICHARD L. SUTTON, JR., M.D., Assistant Professor of Dermatology, University of Kansas Medical School. Pp. 481; 413 illus. St. Louis: C. V. Mosby Company, 1942. Price, $5.50.

The Embryological Treatises of Hieronymus Fabricius of Aquapendente. A facsimile edition, with an introduction, a translation, and a commentary by HOWARD B. ADELMANN, Professor of Histology and Embryology, Cornell University. Pp. 883; 85 figs. Ithaca, N. Y.: Cornell University Press, 1942. Price, $12.00. Reviewed in this issue, p. 879.

Selection of Officer Candidates. 1. Studies in the Relation of Personality to Field of Work. From the Grant Study, Department of Hygiene, Harvard University, WILLIAM L. WOODS, M.D., LUCIEN BROUHA, M.D., CARL C. SELTZER, PH.D. Pp. 46; 10 figs. Cambridge, Mass.: Harvard University Press, 1943. Price, 75 cents.

A short, concise communication with discussion, description and results of methods used and recommended for selection of officer candidates upon the basis of three interrelated tests: 1, physical fitness; 2, short interview; and, 3, "masculine component" evaluation. Charts, graphs and forms used in the method are also included. The monograph should be interesting to those selecting officer candidates. H. H.

Modern Trends in Ophthalmology. Edited by FREDERICK RIDLEY and ARNOLD SORSBY. Pp. 699; 217 figs.; 8 color plates. First published in Great Britain, 1940. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, 1943. Price, $10.00.

Mind, Medicine, and Man. By GREGORY ZILBOORG, M.D. Foreword by ARTHUR H. RUGGLES, M.D. Pp. 344. New York: Harcourt, Brace & Co., 1943. Price, $3.50.

Manual of Industrial Hygiene and Medical Service in War Industries. Edited by WILLIAM M. GAFAFER, D.Sc. Issued under the auspices of the Committee on Industrial Medicine of the Division of Medical Sciences of the National Research Council. Prepared by the Division of Industrial Hygiene, National Institute of Health, U. S. Public Health Service. A composite book with 16 distributors. Pp. 508; 20 illus. Philadelphia and London: W. B. Saunders Company, 1943. Price, $3.00.

NEW EDITIONS

Laboratory Experiments in Physiology. By W. D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). Third ed. Pp. 256; 88 illus. St. Louis: C. V. Mosby Company, 1943. Price, $2.25.

On Growth and Form. By SIR D'ARCY WENTWORTH THOMPSON. Revised and enlarged ed. Pp. 1116; 554 figs. Cambridge: University Press. New York: The Macmillan Company, 1942. Price, $12.50.

Brucellosis in Man and Animals. By I. FOREST HUDDLESON, D.V.M., M.S., PH.D., Research Professor in Bacteriology, Michigan State College. Contributing Authors, A. V. HARDY, M.S., M.D., DR.P.H., Associate Professor of Epidemiology, DeLamar Institute of Public Health, Columbia University Medical School, Consultant, U. S. Public Health Service; J. E. DEBONO, M.D., M.R.C.P., Professor of Pharmacology and Therapeutics, Royal University of Malta; WARD GILTNER, D.V.M., M.S., DR.P.H., Dean of Veterinary Division and Professor of Bacteriology, Michigan State College. Third ed. Pp. 379; 37 figs. New York: The Commonwealth Fund, 1943. Price, $3.50.

Text-book of Pathology. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; Formerly Professor of Pathology in the University of Manitoba, Winnipeg, Canada. Fourth ed. Pp. 1008; 490 engravings (29 colored plates). Philadelphia: Lea & Febiger, 1943. Price, $10.00.

Neurology. By ROY R. GRINKER, M.D., Chairman, The Department of Neuropsychiatry of the Michael Reese Hospital, Chicago. With the assistance of NORMAN A. LEVY, M.D., Associate Neuropsychiatrist, Michael Reese Hospital. Chapter on Brain Tumors by PAUL C. BUCY, M.D., Professor of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago. Third ed. Pp. 1136; 416 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, $6.50.

Primer of Allergy. By WARREN T. VAUGHAN, M.S., M.D., Richmond, Va. With illustrations by JOHN P. TILLERY. Second ed. Pp. 176. St. Louis: C. V. Mosby Company, 1943. Price, $1.75.

This small volume continues to give the allergic patient a general understanding of the nature of allergic diseases in an interesting and delightful manner. It is especially appropriate in that most physicians are unable to take time to discuss in much detail the character of this disease and its management to their patients. The author is aware of the individuality of the practice of medicine, and has, likewise, presented his material with this in mind. This book is well recommended and should find a useful place in both the home and the reception room. M. T.

The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects. By JOHN R. PAUL, M.D., Professor of Preventive Medicine, Yale University School of Medicine, and Other Contributors. Second ed. For the American Heart Assn. Pp. 163; various tables and figs. Printed by the Metropolitan Life Insurance Company. Copies will be sent without charge to physicians upon request. Address inquiries to the American Heart Assn., Inc., 1790 Broadway, New York.

Rheumatic fever, as one of the most important problems of heart disease—in fact, of internal medicine as a whole—has appropriately been the subject of many excellent studies in recent years. These have brought forth so much new information about the varied aspects of the disease since 1928, that again the American Heart Association has published this detailed statement on its epidemiology, the publication having again been made possible by a grant from the Metropolitan Life Insurance Company. Edited and largely composed by one who has himself contributed so much to this phase of the subject, it is the most authoritative statement available, and one that is a necessary tool for all progressive internists and public health specialists.

In this second edition, with a new title, Part I covers its Nomenclature, Definition, a Historical Review, and the relations of the disease to hemolytic streptococcus infection. In Part II, various epidemiological factors are discussed; and in Part III the Public Health aspects. Four appendices on techniques of study precede a list of some 318 recent references.

Though many copies of this edition have apparently already been distributed, a prompt inquiry addressed to the American Heart Association will probably not be in vain. E. K.

Blood Groups and Transfusion. By ALEXANDER S. WIENER, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City, Head of Transfusion Division, Jewish Hospital of Brooklyn, N. Y. Third ed. Pp. 438; 69 figs., 106 tables. Springfield, Ill., and Baltimore, Md.: Charles C Thomas, 1943. Price, $7.50.

Notice to Contributors. Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

Instructions to Contributors. MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

Activated by a directive from the War Production Board, we are changing the size of our type page for the "duration" to effect an economy in the amount of paper used. While there is a lesser number of pages, the amount of material has not been noticeably reduced.

We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.*, conservation of paper.

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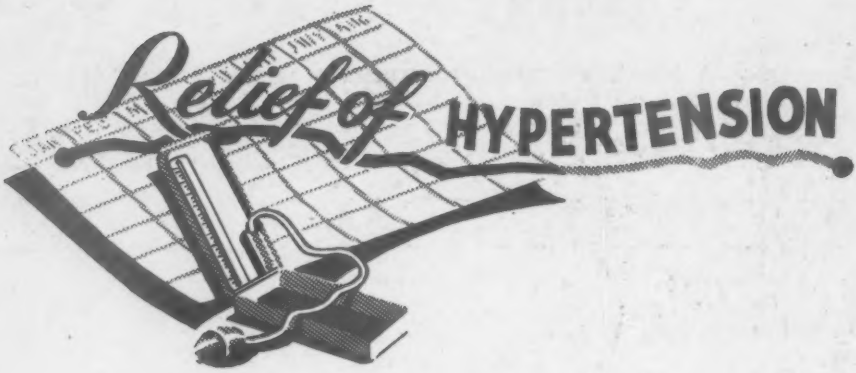

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